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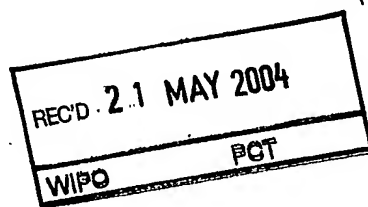
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出 願 年 月 日
Date of Application: 2003年 3月26日

出 願 番 号
Application Number: 特願2003-126022
[ST. 10/C]: [JP 2003-126022]

出 願 人
Applicant(s): 三菱ウェルファーマ株式会社
サノフィーサンテラボ

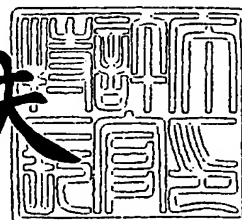


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【書類名】 特許願

【整理番号】 A31199M

【特記事項】 特許法第36条の2第1項の規定による特許出願

【提出日】 平成15年 3月26日

【あて先】 特許庁長官殿

【発明者】

【住所又は居所】 東京都中央区日本橋本町2丁目2番6号 三菱ウェルファーマ株式会社東京本社内

【氏名】 渡邊 和俊

【発明者】

【住所又は居所】 東京都中央区日本橋本町2丁目2番6号 三菱ウェルファーマ株式会社東京本社内

【氏名】 上原 史朗

【発明者】

【住所又は居所】 東京都中央区日本橋本町2丁目2番6号 三菱ウェルファーマ株式会社東京本社内

【氏名】 比企 紳介

【発明者】

【住所又は居所】 東京都中央区日本橋本町2丁目2番6号 三菱ウェルファーマ株式会社東京本社内

【氏名】 横島 聡

【発明者】

【住所又は居所】 東京都中央区日本橋本町2丁目2番6号 三菱ウェルファーマ株式会社東京本社内

【氏名】 臼井 義浩

【発明者】

【住所又は居所】 東京都中央区日本橋本町2丁目2番6号 三菱ウェルファーマ株式会社東京本社内

【氏名】 照田 文

【発明者】

【住所又は居所】 東京都中央区日本橋本町 2 丁目 2 番 6 号 三菱ウェルファーマ株式会社東京本社内

【氏名】 小原 利行

【特許出願人】

【識別番号】 000006725

【氏名又は名称】 三菱ウェルファーマ株式会社

【特許出願人】

【識別番号】 399050909

【氏名又は名称】 サノフィーサンテラボ

【代理人】

【識別番号】 110000109

【氏名又は名称】 特許業務法人特許事務所サイクス

【代表者】 今村 正純

【手数料の表示】

【予納台帳番号】 170347

【納付金額】 35,000円

【その他】 サノフィーサンテラボはフランス国の法律に基づく法人

【提出物件の目録】

【物件名】 外国語明細書 1

【物件名】 外国語要約書 1

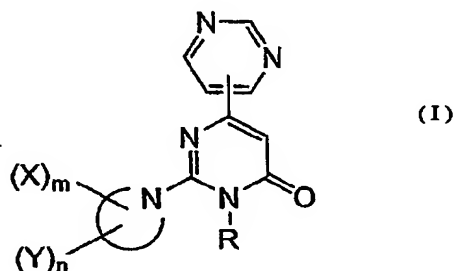
【書類名】 外国語明細書

1. TITLE OF INVENTION

3-SUBSTITUTED-4-PYRIMIDONE DERIVATIVES

2. CLAIMS

1. A pyrimidone derivative represented by formula (I) or a salt thereof, or a solvate thereof or a hydrate thereof:



wherein R represents a C₁-C₁₂ alkyl group which may be substituted;
the ring of:



represents piperazine ring or piperidine ring;

each X independently represents a C₁-C₈ alkyl group which may be substituted, an optionally partially hydrogenated C₆-C₁₀ aryl ring which may be substituted, an indan ring which may be substituted, an optionally substituted heterocyclic ring having 1 to 4 hetero atoms selected from the group consisting of oxygen atom, sulfur atom, and nitrogen atom, and having 5 to 10 ring-constituting atoms in total or X¹-CO- wherein X¹ represents a C₆-C₁₀ aryl ring which may be substituted or a C₁-C₈ alkyl group which may be substituted;

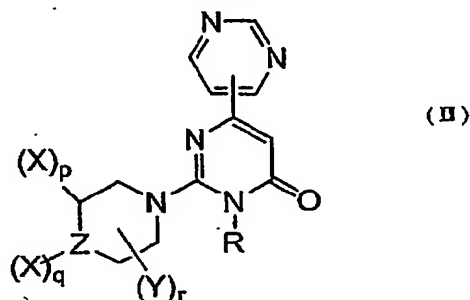
m represents an integer of 1 to 3;

each Y independently represents a halogen atom, a hydroxy group, a cyano group, a C₁-C₈ alkyl group which may be substituted, Y¹-CO- wherein Y¹ represents a C₆-C₁₀ aryl ring which may be substituted or a C₁-C₈ alkyl group which may be substituted or Y²-O-CO- wherein Y² represents a C₁-C₈ alkyl group which may be substituted;
n represents an integer of 0 to 8;

when X and Y or two Y groups are attached on the same carbon atom, they may combine to each other to form a C₂-C₆ alkylene group;
and when m is 1, n is 0 and X is X¹-CO-, then:

- (1) X does not bind to 3-position of unsubstituted 1-piperazinyl group or does not bind to 3-position of a 4-alkyl-1-piperazinyl group; or
- (2) X does not bind to 3-position or 4-position of non-substituted 1-piperidinyl group.

2. The pyrimidone derivative or the salt thereof, or the solvate thereof or the hydrate thereof according to claim 1 having the following formula(II):



wherein R, X and Y are the same as those defined in claim 1;
p is 0 or 1; q is 0 or 1; r is an integer of 0 to 6; p+q is 1 or 2;
and Z represents N or CZ¹ wherein Z¹ represents hydrogen atom or Y.

3. The pyrimidone derivative or the salt thereof, or the solvate thereof or the hydrate thereof according to claim 2, wherein R is a C₁-C₃ alkyl group which may be substituted by a C₃-C₈ cycloalkyl group.

4. The pyrimidone derivative or the salt thereof, or the solvate thereof or the hydrate thereof according to claim 3, wherein R is methyl group or ethyl group; Y is in 3-, 4- or 5-position of the piperazine ring or the piperidine ring; p+q is 1; and r is an integer of 0 to 3.

5. The pyrimidone derivative or the salt thereof, or the solvate thereof or the hydrate thereof according to claim 4, wherein X is a C₁-C₈ alkyl group which may be substituted or a C₆-C₁₀ aryl ring which may be substituted; Y is a C₁-C₆ alkyl group which may be substituted; p is 1; q is 0; r is an integer of 0 to 3; and Z is N or CH.

6. The pyrimidone derivative or the salt thereof, or the solvate thereof or the hydrate thereof according to claim 5, wherein X is a benzene ring which may be substituted, a benzyl group which may be substituted; Y is a methyl group which may be substituted; Z is N and r is 0 or 1.

7. The pyrimidone derivative or the salt thereof, or the solvate thereof or the hydrate thereof according to claim 4, wherein X is a benzene ring which may be substituted, a benzyl group which may be substituted, a benzoyl group which may be substituted, or a benzisothiazol ring which may be substituted; Y is a methyl group which may be substituted; Z is N and p is 0.

8. The pyrimidone derivative or the salt thereof, or the solvate thereof or the hydrate thereof according to claim 4, wherein X is a C₁-C₈ alkyl group substituted by a benzene ring which may be substituted or a benzene ring which may be substituted; Y is a hydroxy group, a cyano group, or Y¹-CO- wherein Y¹ is a C₁-C₈ alkyl group; Z is CH or C-Y and r is 0 or 1.

9. The pyrimidone derivative or the salt thereof, or the solvate thereof or the hydrate thereof according to claim 8, wherein X is a benzyl group which may be substituted or a benzene ring which may be substituted; Y is a hydroxy group, a cyano group, or an acetyl group; Z is CH or C-Y and r is 0 or 1.

10. A pyrimidone derivative which is selected from the group consisting of:
2-(3-Phenylpiperazin-1-yl)-3-methyl-6-(4-pyrimidyl)-3H-pyrimidin-4-one;
2-(3-(4-Fluorophenyl)piperazin-1-yl)-3-methyl-6-(4-pyrimidyl)-3H-pyrimidin-4-one;
2-(3-(3-Fluorophenyl)piperazin-1-yl)-3-methyl-6-(4-pyrimidyl)-3H-pyrimidin-4-one;
2-(3-(2-Fluorophenyl)piperazin-1-yl)-3-methyl-6-(4-pyrimidyl)-3H-pyrimidin-4-one;
2-(3-(4-Chlorophenyl)piperazin-1-yl)-3-methyl-6-(4-pyrimidyl)-3H-pyrimidin-4-one;
2-(3-(3-Chlorophenyl)piperazin-1-yl)-3-methyl-6-(4-pyrimidyl)-3H-pyrimidin-4-one;
2-(3-(2-Chlorophenyl)piperazin-1-yl)-3-methyl-6-(4-pyrimidyl)-3H-pyrimidin-4-one;
2-(3-(4-Bromophenyl)piperazin-1-yl)-3-methyl-6-(4-pyrimidyl)-3H-pyrimidin-4-one;
2-(3-(3-Bromophenyl)piperazin-1-yl)-3-methyl-6-(4-pyrimidyl)-3H-pyrimidin-4-one;
2-(3-(2-Bromophenyl)piperazin-1-yl)-3-methyl-6-(4-pyrimidyl)-3H-pyrimidin-4-one;

2-(3-(4-Cyanophenyl)piperazin-1-yl)-3-methyl-6-(4-pyrimidyl)-3*H*-pyrimidin-4-one;
2-(3-(3-Cyanophenyl)piperazin-1-yl)-3-methyl-6-(4-pyrimidyl)-3*H*-pyrimidin-4-one;
2-(3-(2-Cyanophenyl)piperazin-1-yl)-3-methyl-6-(4-pyrimidyl)-3*H*-pyrimidin-4-one;
2-(3-(4-Methoxyphenyl)piperazin-1-yl)-3-methyl-6-(4-pyrimidyl)-3*H*-pyrimidin-4-one;
2-(3-(3-Methoxyphenyl)piperazin-1-yl)-3-methyl-6-(4-pyrimidyl)-3*H*-pyrimidin-4-one;
2-(3-(2-Methoxyphenyl)piperazin-1-yl)-3-methyl-6-(4-pyrimidyl)-3*H*-pyrimidin-4-one;
2-(3-(2-Ethoxyphenyl)piperazin-1-yl)-3-methyl-6-(4-pyrimidyl)-3*H*-pyrimidin-4-one;
2-(3-(6-Fluoro-2-methoxyphenyl)piperazin-1-yl)-3-methyl-6-(4-pyrimidyl)-3*H*-pyrimidin-4-one;
2-(3-(5-Fluoro-2-methoxyphenyl)piperazin-1-yl)-3-methyl-6-(4-pyrimidyl)-3*H*-pyrimidin-4-one;
2-(3-(4-Fluoro-2-methoxyphenyl)piperazin-1-yl)-3-methyl-6-(4-pyrimidyl)-3*H*-pyrimidin-4-one;
(*S*)-2-(3-(4-Fluoro-2-methoxyphenyl)piperazin-1-yl)-3-methyl-6-(4-pyrimidyl)-3*H*-pyrimidin-4-one;
(*R*)-2-(3-(4-Fluoro-2-methoxyphenyl)piperazin-1-yl)-3-methyl-6-(4-pyrimidyl)-3*H*-pyrimidin-4-one;
2-(3-(4-Chloro-2-methoxyphenyl)piperazin-1-yl)-3-methyl-6-(4-pyrimidyl)-3*H*-pyrimidin-4-one;
2-(3-(5-Bromo-2-methoxyphenyl)piperazin-1-yl)-3-methyl-6-(4-pyrimidyl)-3*H*-pyrimidin-4-one;
2-(3-(2,6-Dichlorophenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3*H*-pyrimidin-4-one;
2-(3-(2,4-Dimethoxyphenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3*H*-pyrimidin-4-one;
2-(3-(3,4-Dimethoxyphenyl)piperazin-1-yl)-3-methyl-6-(4-pyrimidyl)-3*H*-pyrimidin-4-one;
2-(3-(2,5-Dimethoxyphenyl)piperazin-1-yl)-3-methyl-6-(4-pyrimidyl)-3*H*-pyrimidin-4-one;
2-(3-(2,6-Dimethoxyphenyl)piperazin-1-yl)-3-methyl-6-(4-pyrimidyl)-3*H*-

pyrimidin-4-one;
2-(3-(2,4-Difluoro-6-methoxyphenyl)piperazin-1-yl)-3-methyl-6-(4-pyrimidyl)-3H-pyrimidin-4-one;
2-(3-(1-Naphthyl)piperazin-1-yl)-3-methyl-6-(4-pyrimidyl)-3H-pyrimidin-4-one;
2-(3-(2-Naphthyl)piperazin-1-yl)-3-methyl-6-(4-pyrimidyl)-3H-pyrimidin-4-one;
2-(3-(2,3-Dihydrobenzofuran-7-yl)piperazin-1-yl)-3-methyl-6-(4-pyrimidyl)-3H-pyrimidin-4-one;
2-(3-(Benzofuran-2-yl)piperazin-1-yl)-3-methyl-6-(4-pyrimidyl)-3H-pyrimidin-4-one;
2-(3-(4-(Pyrrolidin-1-yl-methyl)phenyl)piperazin-1-yl)-3-methyl-6-(4-pyrimidyl)-3H-pyrimidin-4-one;
2-(3-(4-(Pyrrolidin-1-yl)phenyl)piperazin-1-yl)-3-methyl-6-(4-pyrimidyl)-3H-pyrimidin-4-one;
2-(3-(2-methoxy-4-(pyrrolidin-1-yl)phenyl)piperazin-1-yl)-3-methyl-6-(4-pyrimidyl)-3H-pyrimidin-4-one;
2-(3-(2-methoxy-5-(pyrrolidin-1-yl)phenyl)piperazin-1-yl)-3-methyl-6-(4-pyrimidyl)-3H-pyrimidin-4-one;
2-(3-(4-(Phenyl)phenyl)piperazin-1-yl)-3-methyl-6-(4-pyrimidyl)-3H-pyrimidin-4-one;
2-(3-(4-(4-Fluorophenyl)phenyl)piperazin-1-yl)-3-methyl-6-(4-pyrimidyl)-3H-pyrimidin-4-one;
2-(3-(4-(4-Methoxyphenyl)phenyl)piperazin-1-yl)-3-methyl-6-(4-pyrimidyl)-3H-pyrimidin-4-one;
2-(3-(4-(2-Methoxyphenyl)phenyl)piperazin-1-yl)-3-methyl-6-(4-pyrimidyl)-3H-pyrimidin-4-one;
2-(3-(4-(Morpholin-4-yl)phenyl)piperazin-1-yl)-3-methyl-6-(4-pyrimidyl)-3H-pyrimidin-4-one;
2-(3-(4-(4-Methylpiperazin-1-yl)phenyl)piperazin-1-yl)-3-methyl-6-(4-pyrimidyl)-3H-pyrimidin-4-one;
2-(3-(4-Fluoro-2-methoxyphenyl)-4-methylpiperazin-1-yl)-3-methyl-6-(4-pyrimidyl)-3H-pyrimidin-4-one;
(S)-2-(3-(4-Fluoro-2-methoxyphenyl)-4-methylpiperazin-1-yl)-3-methyl-6-(4-pyrimidyl)-3H-pyrimidin-4-one;
(R)-2-(3-(4-Fluoro-2-methoxyphenyl)-4-methylpiperazin-1-yl)-3-methyl-6-(4-

pyrimidyl)-3 *H*-pyrimidin-4-one;
2-(4-Acetyl-3-(4-fluoro-2-methoxyphenyl)piperazin-1-yl)-3-methyl-6-(4-pyrimidyl)-3 *H*-pyrimidin-4-one;
2-(4-Benzyl-3-(4-fluoro-2-methoxyphenyl)piperazin-1-yl)-3-methyl-6-(4-pyrimidyl)-3 *H*-pyrimidin-4-one;
2-(4-(4-Fluorophenyl)piperidin-1-yl)-3-methyl-6-(4-pyrimidyl)-3 *H*-pyrimidin-4-one;
2-(4-Cyano-4-phenylpiperidin-1-yl)-3-methyl-6-(4-pyrimidyl)-3 *H*-pyrimidin-4-one;
2-(4-(6-Fluorobenofuran-3-yl)piperidin-1-yl)-3-methyl-6-(4-pyrimidyl)-3 *H*-pyrimidin-4-one;
2-(3-(Benzoisoxazol-3-yl)piperidin-1-yl)-3-methyl-6-(4-pyrimidyl)-3 *H*-pyrimidin-4-one;
(*S*)-2-(3-(Benzoisoxazol-3-yl)piperidin-1-yl)-3-methyl-6-(4-pyrimidyl)-3 *H*-pyrimidin-4-one;
(*R*)-2-(3-(Benzoisoxazol-3-yl)piperidin-1-yl)-3-methyl-6-(4-pyrimidyl)-3 *H*-pyrimidin-4-one;
2-(3-(6-Fluorobenzoisoxazol-3-yl)piperidin-1-yl)-3-methyl-6-(4-pyrimidyl)-3 *H*-pyrimidin-4-one;
2-(4-(6-Fluorobenzoisoxazol-3-yl)piperidin-1-yl)-3-methyl-6-(4-pyrimidyl)-3 *H*-pyrimidin-4-one;
2-(4-(5-Methylbenofuran-3-yl)piperidin-1-yl)-3-methyl-6-(4-pyrimidyl)-3 *H*-pyrimidin-4-one; and
2-(4-(6-Fluorobenzothiophene-3-yl)piperidin-1-yl)-3-methyl-6-(4-pyrimidyl)-3 *H*-pyrimidin-4-one
or a salt thereof, or a solvate thereof or a hydrate thereof.

11. A medicament comprising as an active ingredient a substance selected from the group consisting of the pyrimidone derivative represented by formula (I) and a salt thereof, and a solvate thereof and a hydrate thereof according to claim 1.

12. A tau protein kinase 1 inhibitor selected from the group consisting of the pyrimidone derivative represented by formula (I) and a salt thereof, and a solvate thereof and a hydrate thereof according to claim 1.

13. The medicament according to claim 11 which is used for preventive and/or therapeutic treatment of a disease caused by tau protein kinase 1 hyperactivity.

14. The medicament according to claim 11 which is used for preventive and/or therapeutic treatment of a neurodegenerative disease.

15. The medicament according to claim 14, wherein the neurodegenerative disease is selected from the group consisting of Alzheimer disease, ischemic cerebrovascular accidents, Down syndrome, cerebral bleeding due to cerebral amyloid angiopathy, progressive supranuclear palsy, subacute sclerosing panencephalitic parkinsonism, postencephalitic parkinsonism, pugilistic encephalitis, Guam parkinsonism-dementia complex, Lewy body disease, Pick's disease, corticobasal degeneration, frontotemporal dementia, vascular dementia, traumatic injuries, brain and spinal cord trauma, peripheral neuropathies, retinopathies and glaucoma.

16. The medicament according to claim 11, wherein the disease is selected from the group consisting of non-insulin dependent diabetes, obesity, manic depressive illness, schizophrenia, alopecia, breast cancer, non-small cell lung carcinoma, thyroid cancer, T or B-cell leukemia, and a virus-induced tumor.

3. DETAILED DESCRIPTION OF INVENTION

Technical Field

The present invention relates to compounds that are useful as an active ingredient of a medicament for preventive and/or therapeutic treatment of diseases mainly caused by abnormal activity of tau protein kinase 1, such as neurodegenerative diseases (e.g. Alzheimer disease).

Background Art

Alzheimer disease is progressive senile dementia, in which marked cerebral cortical atrophy is observed due to degeneration of nerve cells and decrease of nerve cell number. Pathologically, numerous senile plaques and neurofibrillary tangles are observed in brain. The number of patients has been increased with the increment of aged population, and the disease arises a serious social problem. Although various theories have been proposed, a cause of the disease has not yet been elucidated. Early resolution of the cause has been desired.

It has been known that the degree of appearance of two characteristic

pathological changes of Alzheimer disease well correlates to the degree of intellectual dysfunction. Therefore, researches have been conducted from early 1980's to reveal the cause of the disease through molecular level investigations of components of the two pathological changes. Senile plaques accumulate extracellularly, and β amyloid protein has been elucidated as their main component (abbreviated as " $A\beta$ " hereinafter in the specification: Biochem. Biophys. Res. Commun., 120, 855 (1984); EMBO J., 4, 2757 (1985); Proc. Natl. Acad. Sci. USA, 82, 4245 (1985)). In the other pathological change, i.e., the neurofibrillary tangles, a double-helical filamentous substance called paired helical filament (abbreviated as "PHF" hereinafter in the specification) accumulate intracellularly, and tau protein, which is a kind of microtubule-associated protein specific for brain, has been revealed as its main component (Proc. Natl. Acad. Sci. USA, 85, 4506 (1988); Neuron, 1, 827 (1988)).

Furthermore, on the basis of genetic investigations, presenilins 1 and 2 were found as causative genes of familial Alzheimer disease (Nature, 375, 754 (1995); Science, 269, 973 (1995); Nature, 376, 775 (1995)), and it has been revealed that presence of mutants of presenilins 1 and 2 promotes the secretion of $A\beta$ (Neuron, 17, 1005 (1996); Proc. Natl. Acad. Sci. USA, 94, 2025 (1997)). From these results, it is considered that, in Alzheimer disease, $A\beta$ abnormally accumulates and agglomerates due to a certain reason, which engages with the formation of PHF to cause death of nerve cells. It is also expected that extracellular outflow of glutamic acid and activation of glutamate receptor responding to the outflow may possibly be important factors in an early process of the nerve cell death caused by ischemic cerebrovascular accidents (Sai-shin Igaku [Latest Medicine], 49, 1506 (1994)).

It has been reported that kainic acid treatment that stimulates the AMPA receptor, one of glutamate receptor, increases mRNA of the amyloid precursor protein (abbreviated as "APP" hereinafter in the specification) as a precursor of $A\beta$ (Society for Neuroscience Abstracts, 17, 1445 (1991)), and also promotes metabolism of APP (The Journal of Neuroscience, 10, 2400 (1990)). Therefore, it has been strongly suggested that the accumulation of $A\beta$ is involved in cellular death due to ischemic cerebrovascular disorders. Other diseases in which abnormal

accumulation and agglomeration of A β are observed include, for example, Down syndrome, cerebral bleeding due to solitary cerebral amyloid angiopathy, Lewy body disease (Shin-kei Shinpo [Nerve Advance], 34, 343 (1990); Tanpaku-shitu Kaku-san Koso [Protein, Nucleic Acid, Enzyme], 41, 1476 (1996)) and the like. Furthermore, as diseases showing neurofibrillary tangles due to the PHF accumulation, examples include progressive supranuclear palsy, subacute sclerosing panencephalitic parkinsonism, postencephalitic parkinsonism, pugilistic encephalitis, Guam parkinsonism-dementia complex, Lewy body disease and the like (Tanpakushitu Kakusan Koso [Protein, Nucleic Acid, Enzyme], 36, 2 (1991); Igaku no Ayumi [Progress of Medicine], 158, 511 (1991); Tanpakushitu Kakusan Koso [Protein, Nucleic Acid, Enzyme], 41, 1476 (1996)).

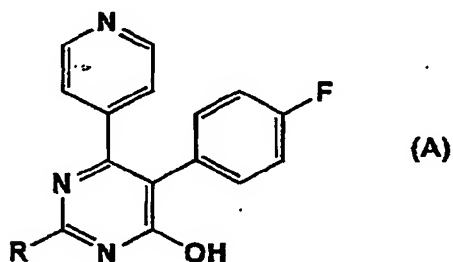
The tau protein is generally composed of a group of related proteins that forms several bands at molecular weights of 48-65 kDa in SDS-polyacrylamide gel electrophoresis, and it promotes the formation of microtubules. It has been verified that tau protein incorporated in the PHF in the brain suffering from Alzheimer disease is abnormally phosphorylated compared with usual tau protein (J. Biochem., 99, 1807 (1986); Proc. Natl. Acad. Sci. USA, 83, 4913 (1986)). An enzyme catalyzing the abnormal phosphorylation has been isolated. The protein was named as tau protein kinase 1 (abbreviated as "TPK1" hereinafter in the specification), and its physicochemical properties have been elucidated (Seikagaku [Biochemistry], 64, 308 (1992); J. Biol. Chem., 267, 10897 (1992)). Moreover, cDNA of rat TPK1 was cloned from a rat cerebral cortex cDNA library based on a partial amino acid sequence of TPK1, and its nucleotide sequence was determined and an amino acid sequence was deduced (Japanese Patent Un-examined Publication [Kokai] No. 6-239893/1994). As a result, it has been revealed that the primary structure of the rat TPK1 corresponds to that of the enzyme known as rat GSK-3 β (glycogen synthase kinase 3 β , FEBS Lett., 325, 167 (1993)).

It has been reported that A β , the main component of senile plaques, is neurotoxic (Science, 250, 279 (1990)). However, various theories have been proposed as for the reason why A β causes the cell death, and any authentic theory has not yet been established. Takashima et al. observed that the cell death was caused by A β treatment of fetal rat hippocampus primary culture system, and then

found that the TPK1 activity was increased by A β treatment and the cell death by A β was inhibited by antisense of TPK1 (Proc. Natl. Acad. Sci. USA, 90, 7789 (1993); Japanese Patent Un-examined Publication [Kokai] No. 6-329551/1994).

In view of the foregoing, compounds which inhibit the TPK1 activity may possibly suppress the neurotoxicity of A β and the formation of PHF and inhibit the nerve cell death in the Alzheimer disease, thereby cease or defer the progress of the disease. The compounds may also be possibly used as a medicament for therapeutic treatment of ischemic cerebrovascular disorder, Down syndrome, cerebral amyloid angiopathy, cerebral bleeding due to Lewy body disease and the like by suppressing the cytotoxicity of A β . Furthermore, the compounds may possibly be used as a medicament for therapeutic treatment of neurodegenerative diseases such as progressive supranuclear palsy, subacute sclerosing panencephalitic parkinsonism, postencephalitic parkinsonism, pugilistic encephalitis, Guam parkinsonism-dementia complex, Lewy body disease, Pick's disease, corticobasal degeneration, frontotemporal dementia, vascular dementia, acute stroke and traumatic injuries, brain and spinal cord trauma, peripheral neuropathies, retinopathies and glaucoma; non-insulin dependent diabetes (such as diabetes type II), and obesity, manic depressive illness, schizophrenia, alopecia, cancers such as breast cancer, non-small cell lung carcinoma, thyroid cancer, T or B-cell leukemia and several virus-induced tumors.

As structurally similar compounds to the compounds of the present invention represented by formula (I) described later, compounds represented by the following formula (A) are known:



wherein R represents 2,6-dichlorobenzyl group, 2-(2-chlorophenyl)ethylamino

group, 3-phenylpropylamino group, or 1-methyl-3-phenylpropylamino group (WO98/24782). The compounds represented by formula (A) are characterized to have 4-fluorophenyl group at the 5-position of the pyrimidine ring and a hydroxy group at the 4-position, and not falling within the scope of the present invention. Moreover, main pharmacological activity of the compounds represented by formula (A) is anti-inflammatory effect, whereas the compounds of the present invention represented by formula (I) are useful as a TPK1 inhibitor or a medicament for therapeutic treatment of neurodegenerative diseases, and therefore, their pharmacological activities are totally different to each other.

Patent Document 1: WO 00/18758

Patent Document 2: WO 01/70728

Patent Document 3: WO 01/70729

Object to be Achieved by the Invention

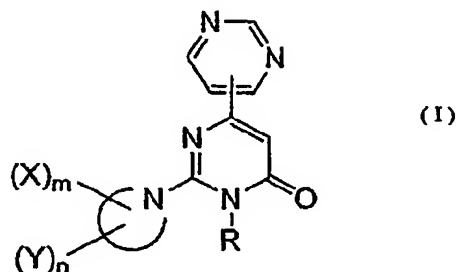
An object of the present invention is to provide compounds useful as an active ingredient of a medicament for preventive and/or therapeutic treatment of diseases such as Alzheimer disease. More specifically, the object is to provide novel compounds useful as an active ingredient of a medicament that enables radical prevention and/or treatment of the neurodegenerative diseases such as Alzheimer disease by inhibiting the TPK1 activity to suppress the neurotoxicity of A β and the formation of the PHF and by inhibiting the death of nerve cells.

Means to Achieve the Object

In order to achieve the foregoing object, the inventors of the present invention conducted screenings of various compounds having inhibitory activity against the phosphorylation of TPK1. As a result, they found that compounds represented by the following formula (I) had the desired activity and were useful as an active ingredient of a medicament for preventive and/or therapeutic treatment of the aforementioned diseases. The present invention was achieved on the basis of these findings.

The present invention thus provides 3-substituted-4-pyrimidone

derivatives represented by formula (I) or salts thereof, or solvates thereof or hydrates thereof:



wherein R represents a C₁-C₁₂ alkyl group which may be substituted;
the ring of:



represents piperazine ring or piperidine ring;

each X independently represents a C₁-C₈ alkyl group which may be substituted, an optionally partially hydrogenated C₆-C₁₀ aryl ring which may be substituted, an indan ring which may be substituted, an optionally substituted heterocyclic ring having 1 to 4 hetero atoms selected from the group consisting of oxygen atom, sulfur atom, and nitrogen atom, and having 5 to 10 ring-constituting atoms in total or X¹-CO- wherein X¹ represents a C₆-C₁₀ aryl ring which may be substituted or a C₁-C₈ alkyl group which may be substituted;

m represents an integer of 1 to 3;

each Y independently represents a halogen atom, a hydroxy group, a cyano group, a C₁-C₆ alkyl group which may be substituted, Y¹-CO- wherein Y¹ represents a C₆-C₁₀ aryl ring which may be substituted or a C₁-C₈ alkyl group which may be substituted or Y²-O-CO- wherein Y² represents a C₁-C₈ alkyl group which may be substituted;

n represents an integer of 0 to 8;

when X and Y or two Y groups are attached on the same carbon atom, they may combine to each other to form a C₂-C₆ alkylene group;

and when m is 1, n is 0 and X is X¹-CO-, then:

- (1) X does not bind to 3-position of unsubstituted 1-piperazinyl group or does not bind to 3-position of a 4-alkyl-1-piperazinyl group; or
- (2) X does not bind to 3-position or 4-position of non-substituted

1-piperidinyl group.

According to another aspect of the present invention, there is provided a medicament comprising as an active ingredient a substance selected from the group consisting of the 3-substituted-4-pyrimidone derivatives represented by formula (I) and the physiologically acceptable salts thereof, and the solvates thereof and the hydrates thereof. As preferred embodiments of the medicament, there are provided the aforementioned medicament which is used for preventive and/or therapeutic treatment of diseases caused by tau protein kinase 1 hyperactivity, and the aforementioned medicament which is used for preventive and/or therapeutic treatment of neurodegenerative diseases.

As further preferred embodiments of the present invention, there are provided the aforementioned medicament wherein the diseases are selected from the group consisting of Alzheimer disease, ischemic cerebrovascular accidents, Down syndrome, cerebral bleeding due to cerebral amyloid angiopathy, progressive supranuclear palsy, subacute sclerosing panencephalitic parkinsonism, postencephalitic parkinsonism, pugilistic encephalitis, Guam parkinsonism-dementia complex, Lewy body disease, Pick's disease, corticobasal degeneration and frontotemporal dementia, vascular dementia, acute stroke and traumatic injuries, brain and spinal cord trauma, peripheral neuropathies, retinopathies and glaucoma, non-insulin dependent diabetes (such as diabetes type II), and obesity, manic depressive illness, schizophrenia, alopecia, cancers such as breast cancer, non-small cell lung carcinoma, thyroid cancer, T or B-cell leukemia and several virus-induced tumors; and the aforementioned medicament in the form of pharmaceutical composition containing the above substance as an active ingredient together with one or more pharmaceutical additives.

The present invention further provides an inhibitor of tau protein kinase 1 comprising as an active ingredient a substance selected from the group consisting of the 3-substituted-4-pyrimidone derivatives of formula (I) and the salts thereof, and the solvates thereof and the hydrates thereof.

According to further aspects of the present invention, there are provided a method for preventive and/or therapeutic treatment of diseases caused by tau

protein kinase 1 hyperactivity, which comprises the step of administering to a patient a preventively and/or therapeutically effective amount of a substance selected from the group consisting of the 3-substituted-4-pyrimidone derivatives of formula (I) and the physiologically acceptable salts thereof, and the solvates thereof and the hydrates thereof; and a use of a substance selected from the group consisting of the 3-substituted-4-pyrimidone derivatives of formula (I) and the physiologically acceptable salts thereof, and the solvates thereof and the hydrates thereof for the manufacture of the aforementioned medicament.

Mode for Carrying Out the Invention

The alkyl group used herein may be either linear or branched.

The C₁-C₁₂ alkyl group represented by R may be, for example, methyl group, ethyl group, n-propyl group, isopropyl group, n-butyl group, isobutyl group, sec-butyl group, tert-butyl group, n-pentyl group, isopentyl group, neopentyl group, 1,1-dimethylpropyl group, n-hexyl group, isohexyl group, or a linear or branched heptyl group, octyl group, nonyl group, decyl group, undecyl group or dodecyl group. Particularly preferred R is methyl group.

In the specification, when a functional group is defined as "which may be substituted" or "optionally substituted", the number of substituents as well as their types and substituting positions are not particularly limited, and when two or more substituents are present, they may be the same or different.

When the C₁-C₁₂ alkyl group represented by R has one or more substituents, the alkyl group may have one or more substituents selected from, for example, the groups consisting of a C₃-C₈ cycloalkyl group such as cyclopropyl group, cyclobutyl group, cyclopentyl group, cyclohexyl group, cycloheptyl group, cyclooctyl group; a C₁-C₅ alkoxy group such as methoxy group, ethoxy group, propoxy group, isopropoxy group, butoxy group, isobutoxy group, tert-butoxy group; C₁-C₃ alkylamino group or C₂-C₆ dialkylamino group; a C₆-C₁₀ aryl group such as phenyl group, 1-naphthyl group, and 2-naphthyl group.

The C₁-C₈ alkyl group represented by X may be, for example, methyl group, ethyl group, n-propyl group, isopropyl group, n-butyl group, isobutyl group, sec-butyl group, tert-butyl group, n-pentyl group, isopentyl group, neopentyl group,

1,1-dimethylpropyl group, n-hexyl group, isohexyl group, or a linear or branched heptyl group or octyl group.

The optionally partially hydrogenated C₆-C₁₀ aryl ring represented by X may be, for example, a benzene ring, a naphthalene ring, an indan ring or a 1,2,3,4-tetrahydronaphthalene ring.

The heterocyclic ring having 1 to 4 hetero atoms selected from the group consisting of oxygen atom, sulfur atom, and nitrogen atom, and having 5 to 10 ring-constituting atoms in total represented by X may be, for example, furan ring, dihydrofuran ring, tetrahydrofuran ring, pyran ring, dihydropyran ring, tetrahydropyran ring, benzofuran ring, dihydrobenzofuran, isobenzofuran ring, benzodioxol ring, chromene ring, chroman ring, isochroman ring, thiophene ring, benzothiophene ring, pyrrole ring, pyrroline ring, pyrrolidine ring, imidazole ring, imidazoline ring, imidazolidine ring, pyrazole ring, pyrazoline ring, pyrazolidine ring, triazole ring, tetrazole ring, pyridine ring, pyridine oxide ring, piperidine ring, pyrazine ring, piperazine ring, pyrimidine ring, pyridazine ring, indole ring, indoline ring, isoindole ring, isoindoline ring, indazole ring, benzimidazole ring, benzotriazole ring, tetrahydroisoquinoline ring, benzothiazolinone ring, benzoxazolinone ring, purine ring, quinolizine ring, quinoline ring, phthalazine ring, naphthyridine ring, quinoxaline ring, quinazoline ring, cinnoline ring, pteridine ring, oxazole ring, oxazolidine ring, isoxazole ring, isoxazolidine ring, oxadiazole ring, thiazole ring, benzothiazole ring, thiazylidine ring, isothiazole ring, isothiazolidine ring, benzodioxole ring, dioxane ring, benzodioxane ring, dithian ring, morpholine ring, thiomorpholine ring, or phthalimide ring.

The C₆-C₁₀ aryl ring represented by X¹ or Y¹ may be, for example, a benzene ring or a naphthalene ring.

When the ring represented by X or X¹ has one or more substituents, the ring may have one or more substituents selected from the group consisting of a C₁-C₅ alkyl group such as methyl group, ethyl group, propyl group, isopropyl group, butyl group, isobutyl group, sec-butyl group, tert-butyl group, pentyl group, isopentyl group, neopentyl group, 1,1-dimethylpropyl group; C₃-C₆ cycloalkyl group such as cyclopropyl group, cyclobutyl group, cyclopentyl group, cyclohexyl group; a C₃-C₆ cycloalkyloxy group such as cyclopropyloxy group, cyclobutyloxy group,

cyclopentyloxy group, cyclohexyloxy group; a C₁-C₅ alkoxy group such as methoxy group, ethoxy group, propoxy group, isopropoxy group, butoxy group, isobutoxy group, tert-butoxy group, pentyloxy group, and isopentyloxy group; a C₄-C₇ cycloalkylalkoxyl group such as cyclopropylmethoxy group, cyclopentylmethoxy group; a C₁-C₅ alkylthio group such as methylthio group, ethylthio group, propylthio group, butylthio group, and pentylthio group; a C₁-C₅ alkylsulfonyl group such as methanesulfonyl group, ethanesulfonyl group, propanesulfonyl group, butanesulfonyl group, and pentanesulfonyl group; a halogen atom such as fluorine atom, chlorine atom, bromine atom, and iodine atom; a C₁-C₅ halogenated alkyl group such as trifluoromethyl group; hydroxyl group; cyano group; nitro group; formyl group; a C₂-C₆ alkylcarbonyl group such as acetyl group, propionyl group, butyryl group, and valeryl group; a benzene ring which may be substituted, a naphthalene ring which may be substituted, an optionally substituted heterocyclic ring having 1 to 4 hetero atoms selected from the group consisting of oxygen atom, sulfur atom and nitrogen atom, and having 5 to 10 ring-constituting atoms in total; a phenoxy group which may be substituted; a phenylamino group which may be substituted; an amino group; a C₁-C₅ monoalkylamino group such as methylamino group, ethylamino group, propylamino group, isopropylamino group, butylamino group, isobutylamino group, tert-butylamino group, pentylamino group, and isopentylamino group; a C₂-C₁₀ dialkylamino group such as dimethylamino group, ethylmethylamino group, diethylamino group, methylpropylamino group, and diisopropylamino group; a C₁-C₅ monoalkylaminomethyl group such as methylaminomethyl group, ethylaminomethyl group, propylaminomethyl group, isopropylaminomethyl group, butylaminomethyl group, isobutylaminomethyl group, tert-butylaminomethyl group, pentylaminomethyl group, isopentylaminomethyl; a C₂-C₁₀ dialkylaminomethyl group such as dimethylaminomethyl group, diethylaminomethyl group, ethylmethylaminomethyl group, methylpropylaminomethyl group; pyrrolidinylmethyl group; piperidinylmethyl group; morpholinomethyl group; piperazinylmethyl group; pyrrolylmethyl group; imidazolylmethyl group; pyrazolylmethyl group; and triazolylmethyl group.

When the C₆-C₁₀ aryl ring represented by Y¹ has one or more substituents, the ring may be substituted by one or more substituents selected from the groups

consisting of halogen atoms, a C₁-C₅ alkyl group, a C₃-C₆ cycloalkyl group, a C₃-C₆ cycloalkyloxy group, a C₁-C₅ alkoxy group, a C₄-C₇ cycloalkylalkoxy, a C₁-C₅ alkylthio group, a C₁-C₅ alkylsulfonyl group, a C₁-C₅ halogenated alkyl, and a benzene ring.

When the ring represented by X, X¹ or Y¹ has one or more substituents, the substituent may further have one or more substituents selected from the group consisting of a C₁-C₅ alkyl group such as methyl group, ethyl group, propyl group, isopropyl group, butyl group, isobutyl group, sec-butyl group, tert-butyl group, pentyl group, isopentyl group, neopentyl group, 1,1-dimethylpropyl group; C₃-C₆ cycloalkyl group such as cyclopropyl group, cyclobutyl group, cyclopentyl group, cyclohexyl group; a C₃-C₆ cycloalkyloxy group such as cyclopropyloxy group, cyclobutyloxy group, cyclopentyloxy group, cyclohexyloxy group; hydroxy group; a C₁-C₅ alkoxy group such as methoxy group, ethoxy group, propoxy group, isopropoxy group, butoxy group, isobutoxy group, tert-butoxy group, pentyloxy group, and isopentyloxy group; a C₄-C₇ cycloalkylalkoxy group such as cyclopropylmethoxy group, cyclopentylmethoxy group; a C₁-C₅ alkylthio group such as methylthio group, ethylthio group, propylthio group, butylthio group, and pentylthio group; a C₁-C₅ alkylsulfonyl group such as methanesulfonyl group, ethanesulfonyl group, propanesulfonyl group, butanesulfonyl group, and pentanesulfonyl group; a halogen atom such as fluorine atom, chlorine atom, bromine atom, and iodine atom; a C₁-C₅ halogenated alkyl group such as trifluoromethyl group; a C₁-C₅ halogenated alkoxy group such as trifluoromethoxy group, 2,2,2-trifluoroethoxy group; hydroxyl group; cyano group; nitro group; formyl group; a C₂-C₆ alkylcarbonyl group such as acetyl group, propionyl group, butyryl group, and valeryl group; amino group; a C₁-C₅ monoalkylamino group such as methylamino group, ethylamino group, propylamino group, isopropylamino group, butylamino group, isobutylamino group, tert-butylamino group, pentylamino group, and isopentylamino group; a C₂-C₁₀ dialkylamino group such as dimethylamino group, ethylmethylamino group, diethylamino group, methylpropylamino group, and diisopropylamino group; a C₂-C₁₀ monoalkylaminomethyl group such as methylaminomethyl group, ethylaminomethyl group, propylaminomethyl group, isopropylaminomethyl group, butylaminomethyl group, isobutylaminomethyl group, tert-butylaminomethyl

group, pentylaminomethyl group, isopentylaminomethyl; a C₃-C₁₁ dialkylaminomethyl group such as dimethylaminomethyl group, diethylaminomethyl group, ethylmethylaminomethyl group, methylpropylaminomethyl group and the like.

R may preferably be a C₁-C₃ alkyl group, more preferably a methyl group or an ethyl group. The substituent of the alkyl group may preferably be a C₃-C₈ alkyl group.

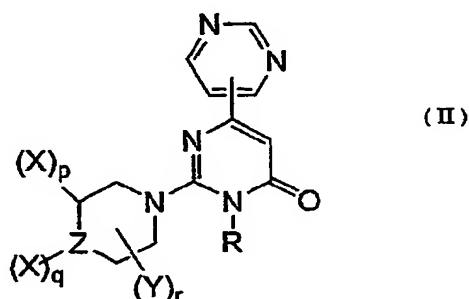
X may preferably be a benzene ring which may be substituted, a benzyl group which may be substituted, a naphthyl group which may be substituted, a benzofuran ring which may be substituted, a dihydrobenzofuran ring which may be substituted, a benzothiophene ring which may be substituted, a benzoxazole ring which may be substituted and a benzisoxazole ring which may be substituted; more preferably a benzene ring which may be substituted, a benzyl group which may be substituted. Substituent of X may preferably be selected from the group of a halogen atom, a C₁-C₄ alkyl group, a C₁-C₄ alkoxy group, a hydroxy group, a nitro group, a cyano group, a C₁-C₄ perhalogenated C₁-C₄ alkyl group, a carboxyl group, a C₁-C₄ alkoxycarbonyl group, a C₁-C₄ alkylthio group, a C₁-C₄ alkoxysulfonyl group and amino group which may be substituted by a C₁-C₄ alkyl group.

The compounds represented by the aforementioned formula (I) may form a salt. Examples of the salt include, when an acidic group exists, salts of alkali metals and alkaline earth metals such as lithium, sodium, potassium, magnesium, and calcium; salts of ammonia and amines such as methylamine, dimethylamine, trimethylamine, dicyclohexylamine, tris(hydroxymethyl)aminomethane, N,N-bis(hydroxyethyl)piperazine, 2-amino-2-methyl-1-propanol, ethanolamine, N-methylglucamine, and L-glucamine; or salts with basic amino acids such as lysine, δ -hydroxylysine, and arginine. When a basic group exists, examples include salts with mineral acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid; salts with organic acids such as methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, acetic acid, propionic acid, tartaric acid, fumaric acid, maleic acid, malic acid, oxalic acid, succinic acid, citric acid, benzoic acid, mandelic acid, cinnamic acid, lactic acid, glycolic acid, glucuronic acid, ascorbic acid, nicotinic acid, and salicylic acid; or

salts with acidic amino acids such as aspartic acid, and glutamic acid.

In addition to the 3-substituted-4-pyrimidone derivatives represented by the aforementioned formula (I) and salts thereof, their solvates and hydrates also fall within the scope of the present invention. The 3-substituted-4-pyrimidone derivatives represented by the aforementioned formula (I) may have one or more asymmetric carbon atoms. As for the stereochemistry of such asymmetric carbon atoms, they may independently be in either (R) and (S) configuration, and the pyrimidone derivative may exist as stereoisomers such as optical isomers, or diastereoisomers. Any stereoisomers in a pure form, any mixtures of stereoisomers, racemates and the like fall within the scope of the present invention.

Preferred compounds of the present invention are represented by formula (II)



wherein R, X, Y are the same as those defined above; p is 0 or 1; q is 0 or 1; r is an integer of 0 to 6; p+q is 1 or 2;

and Z represents N or CZ¹ wherein Z¹ represents hydrogen atom or Y.

Examples of more preferred classes of compounds represented by formula (II) include:

- (1) those wherein R represents a C₁-C₃ alkyl group which may be substituted by a C₃-C₈ cycloalkyl group;
- (2) the compounds of the above (1) wherein R is a methyl group or an ethyl group; Y is in 3-, 4- or 5-position of the piperazine ring or the piperidine ring; p+q is 1; and r is an integer of 0 to 3;
- (3) the compounds of the above (2) wherein X is a C₁-C₈ alkyl group which may be substituted or a C₆-C₁₀ aryl ring which may be substituted; Y is a C₁-C₆ alkyl group which may be substituted; p is 1; q is 0; r is an integer of 0 to 3; and Z is N or CH;
- (4) the compounds of the above (3) wherein X is a benzene ring which may be

substituted, a benzyl group which may be substituted; Y is a methyl group which may be substituted; Z is N and r is 0 or 1;

(5) the compounds of the above (2) wherein X is a benzene ring which may be substituted, a benzyl group which may be substituted, a benzoyl group which may be substituted, or a benzisothiazol ring which may be substituted; Y is a methyl group which may be substituted; Z is N and p is 0;

(6) the compounds of the above (2) wherein X is a C₁-C₈ alkyl group substituted by a benzene ring which may be substituted or a benzene ring which may be substituted; Y is a hydroxy group, a cyano group, or Y¹-CO- wherein Y¹ is a C₁-C₈ alkyl group; Z is CH or C-Y and r is 0 or 1; and

(7) the compounds of the above (6) wherein X is a benzyl group which may be substituted or a benzene ring which may be substituted; Y is a hydroxy group, a cyano group, or an acetyl group; Z is CH or C-Y and r is 0 or 1.

Examples of particularly preferred classes of compounds represented by formula (II) include:

(1) those wherein R is methyl group, Y is CH₃O-CO- group or CH₃CH₂O-CO- group, Z is N, p is 0, q is 1, r is 0 or 1 and Y is in 3-position of the piperazine ring;

(2) those wherein R is methyl group, Y is methyl group, benzyl group or acetyl group, Z is N, p is 1, q is 0, r is 0 or 1 and Y is in 4-position of the piperazine ring;

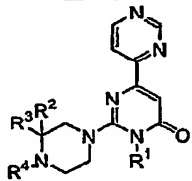






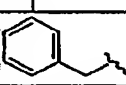
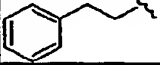
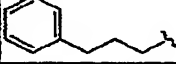



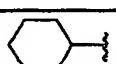
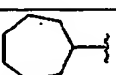



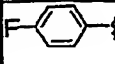

(3) those wherein R is methyl group, Y is methyl group, Z is N, p is 1, q is 0, r is 1 to 3 and Y is in 3-, 4-, or 5-position of the piperazine ring;

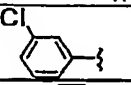
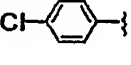

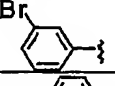
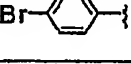


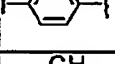
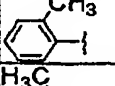
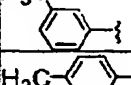
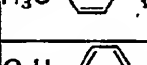
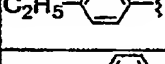
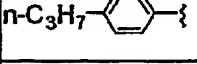
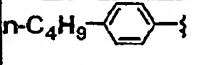

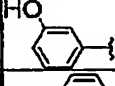
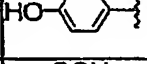
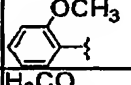
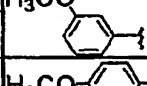
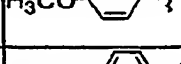
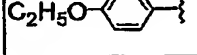
(4) those wherein R is methyl group, Y is hydroxyl group or cyano group, Z is CH, p is 1, q is 0, r is 0 or 1 and X and Y are attached on the same carbon atom;

(4) those wherein R is methyl group, Y is hydroxyl group, cyano group or acetyl group, Z is C-Y, p is 0, q is 1 and r is 1.

Examples of preferred compounds of the present invention are shown in the tables below. However, the scope of the present invention is not limited to the following compounds.

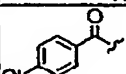
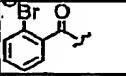
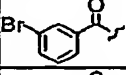
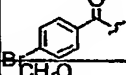
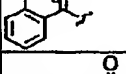
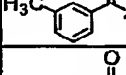
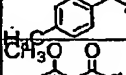
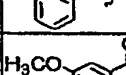
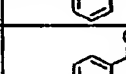
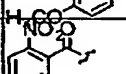
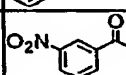
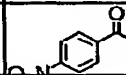
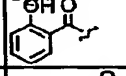
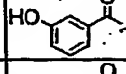
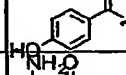
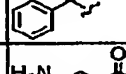
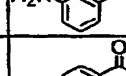
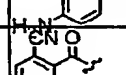
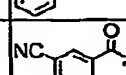


Table-1

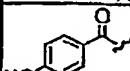
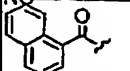
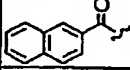
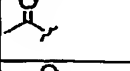
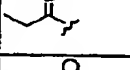
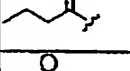
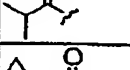
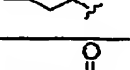
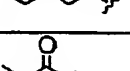
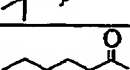
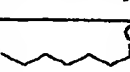
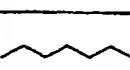
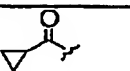
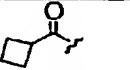
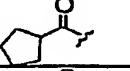
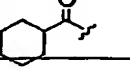

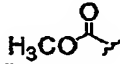
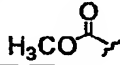
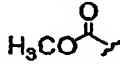
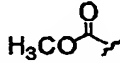
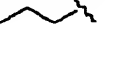
				
No.	R1	R2	R3	R4
A0001	CH3-	H	H	CH3-
A0002	CH3-	H	H	CH3CH2-
A0003	CH3-	H	H	
A0004	CH3-	H	H	
A0005	CH3-	H	H	
A0006	CH3-	H	H	
A0007	CH3-	H	H	
A0008	CH3-	H	H	
A0009	CH3-	H	H	
A0010	CH3-	H	H	
A0011	CH3-	H	H	
A0012	CH3-	H	H	
A0013	CH3-	H	H	
A0014	CH3-	H	H	
A0015	CH3-	H	H	
A0016	CH3-	H	H	
A0017	CH3-	H	H	
A0018	CH3-	H	H	
A0019	CH3-	H	H	
A0020	CH3-	H	H	
A0021	CH3-	H	H	

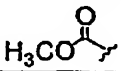

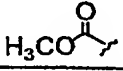

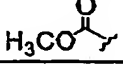

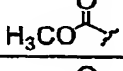

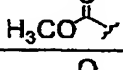

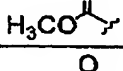
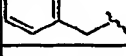
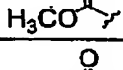

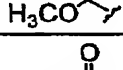
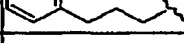
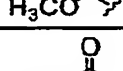

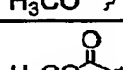

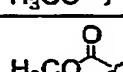

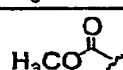

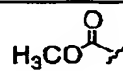
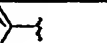
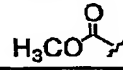

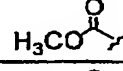

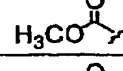

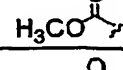

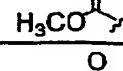

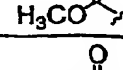

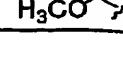



No.	R1	R2	R3	R4
A0022	CH ₃ -	H	H	
A0023	CH ₃ -	H	H	
A0024	CH ₃ -	H	H	
A0025	CH ₃ -	H	H	
A0026	CH ₃ -	H	H	
A0027	CH ₃ -	H	H	
A0028	CH ₃ -	H	H	
A0029	CH ₃ -	H	H	
A0030	CH ₃ -	H	H	
A0031	CH ₃ -	H	H	
A0032	CH ₃ -	H	H	
A0033	CH ₃ -	H	H	
A0034	CH ₃ -	H	H	
A0035	CH ₃ -	H	H	
A0036	CH ₃ -	H	H	
A0037	CH ₃ -	H	H	
A0038	CH ₃ -	H	H	
A0039	CH ₃ -	H	H	
A0040	CH ₃ -	H	H	
A0041	CH ₃ -	H	H	
A0042	CH ₃ -	H	H	

No.	R1	R2	R3	R4
A0043	CH ₃ -	H	H	
A0044	CH ₃ -	H	H	
A0045	CH ₃ -	H	H	
A0046	CH ₃ -	H	H	
A0047	CH ₃ -	H	H	
A0048	CH ₃ -	H	H	
A0049	CH ₃ -	H	H	
A0050	CH ₃ -	H	H	
A0051	CH ₃ -	H	H	
A0052	CH ₃ -	H	H	
A0053	CH ₃ -	H	H	
A0054	CH ₃ -	H	H	
A0055	CH ₃ -	H	H	
A0056	CH ₃ -	H	H	
A0057	CH ₃ -	H	H	
A0058	CH ₃ -	H	H	
A0059	CH ₃ -	H	H	
A0060	CH ₃ -	H	H	
A0061	CH ₃ -	H	H	
A0062	CH ₃ -	H	H	
A0063	CH ₃ -	H	H	

No.	R1	R2	R3	R4
A0064	CH ₃ -	H	H	
A0065	CH ₃ -	H	H	
A0066	CH ₃ -	H	H	
A0067	CH ₃ -	H	H	
A0068	CH ₃ -	H	H	
A0069	CH ₃ -	H	H	
A0070	CH ₃ -	H	H	
A0071	CH ₃ -	H	H	
A0072	CH ₃ -	H	H	
A0073	CH ₃ -	H	H	
A0074	CH ₃ -	H	H	
A0075	CH ₃ -	H	H	
A0076	CH ₃ -	H	H	
A0077	CH ₃ -	H	H	
A0078	CH ₃ -	H	H	
A0079	CH ₃ -	H	H	
A0080	CH ₃ -	H	H	
A0081	CH ₃ -	H	H	
A0082	CH ₃ -	H	H	
A0083	CH ₃ -	H	H	
A0084	CH ₃ -	H	H	

No.	R1	R2	R3	R4
A0085	CH ₃ -	H	H	
A0086	CH ₃ -	H	H	
A0087	CH ₃ -	H	H	
A0088	CH ₃ -	H	H	
A0089	CH ₃ -	H	H	
A0090	CH ₃ -	H	H	
A0091	CH ₃ -	H	H	
A0092	CH ₃ -	H	H	
A0093	CH ₃ -	H	H	
A0094	CH ₃ -	H	H	
A0095	CH ₃ -	H	H	
A0096	CH ₃ -	H	H	
A0097	CH ₃ -	H	H	
A0098	CH ₃ -	H	H	
A0099	CH ₃ -	H	H	
A0100	CH ₃ -	H	H	
A0101	CH ₃ -	H	H	
A0102	CH ₃ -	H	H	
A0103	CH ₃ -	H	H	
A0104	CH ₃ -	H	H	
A0105	CH ₃ -	H	H	

No.	R1	R2	R3	R4
A0106	CH ₃ -	H	H	
A0107	CH ₃ -	H	H	
A0108	CH ₃ -	H	H	
A0109	CH ₃ -	H	H	
A0110	CH ₃ -	H	H	
A0111	CH ₃ -	H	H	
A0112	CH ₃ -	H	H	
A0113	CH ₃ -	H	H	
A0114	CH ₃ -	H	H	
A0115	CH ₃ -	H	H	
A0116	CH ₃ -	H	H	
A0117	CH ₃ -	H	H	
A0118	CH ₃ -	H	H	
A0119	CH ₃ -	H	H	
A0120	CH ₃ -	H	H	
A0121	CH ₃ -	H	H	
A0122	CH ₃ -	H	H	
A0123	CH ₃ -		H	H
A0124	CH ₃ -		H	CH ₃ -
A0125	CH ₃ -		H	CH ₃ CH ₂ -
A0126	CH ₃ -		H	

No.	R1	R2	R3	R4
A0127	CH ₃ -		H	
A0128	CH ₃ -		H	
A0129	CH ₃ -		H	
A0130	CH ₃ -		H	
A0131	CH ₃ -		H	
A0132	CH ₃ -		H	
A0133	CH ₃ -		H	
A0134	CH ₃ -		H	
A0135	CH ₃ -		H	
A0136	CH ₃ -		H	
A0137	CH ₃ -		H	
A0138	CH ₃ -		H	
A0139	CH ₃ -		H	
A0140	CH ₃ -		H	
A0141	CH ₃ -		H	
A0142	CH ₃ -		H	
A0143	CH ₃ -		H	
A0144	CH ₃ -		H	
A0145	CH ₃ -		H	
A0146	CH ₃ -		H	
A0147	CH ₃ -		H	






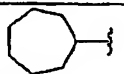





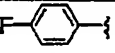
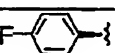
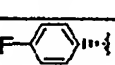

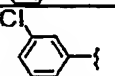
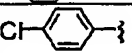

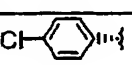

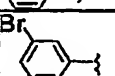
No.	R1	R2	R3	R4
A0148	CH ₃ -		H	
A0149	CH ₃ -		H	
A0150	CH ₃ -		H	
A0151	CH ₃ -		H	
A0152	CH ₃ -		H	
A0153	CH ₃ -		H	
A0154	CH ₃ -		H	
A0155	CH ₃ -		H	
A0156	CH ₃ -		H	
A0157	CH ₃ -		H	
A0158	CH ₃ -		H	
A0159	CH ₃ -		H	
A0160	CH ₃ -		H	
A0161	CH ₃ -		H	
A0162	CH ₃ -		H	
A0163	CH ₃ -		H	
A0164	CH ₃ -		H	
A0165	CH ₃ -		H	
A0166	CH ₃ -		H	
A0167	CH ₃ -		H	
A0168	CH ₃ -		H	

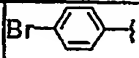
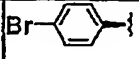
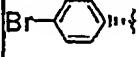
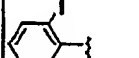
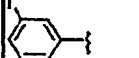
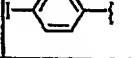
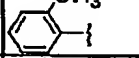
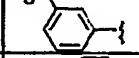
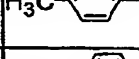
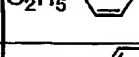
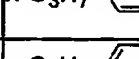
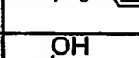
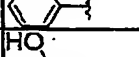
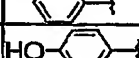
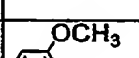
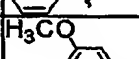
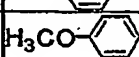
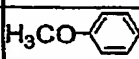
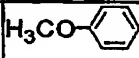
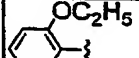

No.	R1	R2	R3	R4
A0169	CH3-		H	
A0170	CH3-		H	
A0171	CH3-		H	
A0172	CH3-		H	
A0173	CH3-		H	
A0174	CH3-		H	
A0175	CH3-		H	
A0176	CH3-		H	
A0177	CH3-		H	
A0178	CH3-		H	H
A0179	CH3-		H	CH3-
A0180	CH3-		H	CH3CH2-
A0181	CH3-		H	
A0182	CH3-		H	
A0183	CH3-		H	
A0184	CH3-		H	
A0185	CH3-		H	
A0186	CH3-		H	
A0187	CH3-		H	
A0188	CH3-		H	
A0189	CH3-		H	

No.	R1	R2	R3	R4
A0190	CH ₃ -		H	
A0191	CH ₃ -		H	
A0192	CH ₃ -		H	
A0193	CH ₃ -		H	
A0194	CH ₃ -		H	
A0195	CH ₃ -		H	
A0196	CH ₃ -		H	
A0197	CH ₃ -		H	
A0198	CH ₃ -		H	
A0199	CH ₃ -		H	
A0200	CH ₃ -		H	
A0201	CH ₃ -		H	
A0202	CH ₃ -		H	
A0203	CH ₃ -		H	
A0204	CH ₃ -		H	
A0205	CH ₃ -		H	
A0206	CH ₃ -		H	
A0207	CH ₃ -		H	
A0208	CH ₃ -		H	
A0209	CH ₃ -		H	
A0210	CH ₃ -		H	

No.	R1	R2	R3	R4
A0211	CH ₃ -		H	
A0212	CH ₃ -		H	
A0213	CH ₃ -		H	
A0214	CH ₃ -		H	
A0215	CH ₃ -		H	
A0216	CH ₃ -		H	
A0217	CH ₃ -		H	
A0218	CH ₃ -		H	
A0219	CH ₃ -		H	
A0220	CH ₃ -		H	
A0221	CH ₃ -		H	
A0222	CH ₃ -		H	
A0223	CH ₃ -		H	
A0224	CH ₃ -		H	
A0225	CH ₃ -		H	
A0226	CH ₃ -		H	
A0227	CH ₃ -		H	
A0228	CH ₃ -		H	
A0229	CH ₃ -		H	
A0230	CH ₃ -		H	
A0231	CH ₃ -		H	

No.	R1	R2	R3	R4
A0232	CH3-		H	
A0233	CH3-	CH3-	H	H
A0234	CH3-	CH3CH2-	H	H
A0235	CH3-		H	H
A0236	CH3-		H	H
A0237	CH3-		H	H
A0238	CH3-		H	H
A0239	CH3-		H	H
A0240	CH3-		H	H
A0241	CH3-		H	H
A0242	CH3-		H	H
A0243	CH3-		H	H
A0244	CH3-		H	H
A0245	CH3-		H	H
A0246	CH3-		H	H
A0247	CH3-		H	H
A0248	CH3-		H	H
A0249	CH3-		H	H
A0250	CH3-		H	H
A0251	CH3-		H	H
A0252	CH3-		H	H


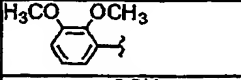
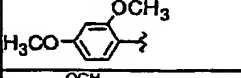
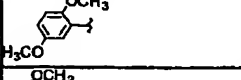
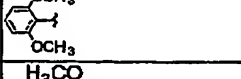
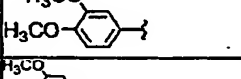
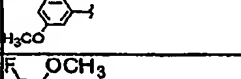
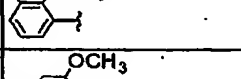
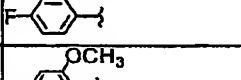
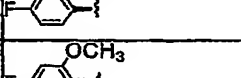
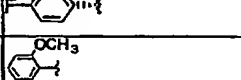
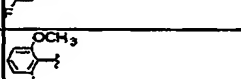
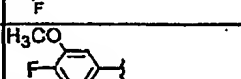
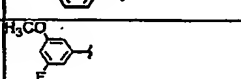
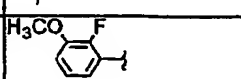
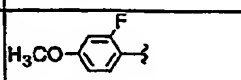
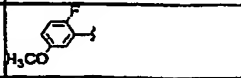
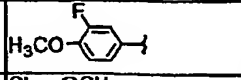
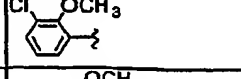
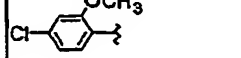

No.	R1	R2	R3	R4
A0253	CH3-		H	H
A0254	CH3-		H	H
A0255	CH3-		H	H
A0256	CH3-		H	H
A0257	CH3-		H	H
A0258	CH3-		H	H
A0259	CH3-		H	H
A0260	CH3-		H	H
A0261	CH3-		H	H
A0262	CH3-		H	H
A0263	CH3-		H	H
A0264	CH3-		H	H
A0265	CH3-		H	H
A0266	CH3-		H	H
A0267	CH3-		H	H
A0268	CH3-		H	H
A0269	CH3-		H	H
A0270	CH3-		H	H
A0271	CH3-		H	H
A0272	CH3-		H	H
A0273	CH3-		H	H



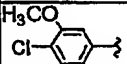

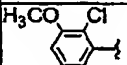
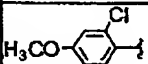

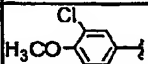
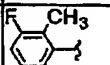
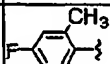


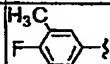

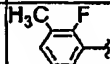
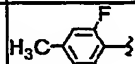

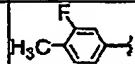
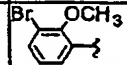
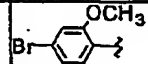

No.	R1	R2	R3	R4
A0274	CH ₃ -		H	H
A0275	CH ₃ -		H	H
A0276	CH ₃ -		H	H
A0277	CH ₃ -		H	H
A0278	CH ₃ -		H	H
A0279	CH ₃ -		H	H
A0280	CH ₃ -		H	H
A0281	CH ₃ -		H	H
A0282	CH ₃ -		H	H
A0283	CH ₃ -		H	H
A0284	CH ₃ -		H	H
A0285	CH ₃ -		H	H
A0286	CH ₃ -		H	H
A0287	CH ₃ -		H	H
A0288	CH ₃ -		H	H
A0289	CH ₃ -		H	H
A0290	CH ₃ -		H	H
A0291	CH ₃ -		H	H
A0292	CH ₃ -		H	H
A0293	CH ₃ -		H	H
A0294	CH ₃ -		H	H


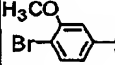
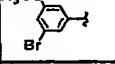
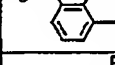
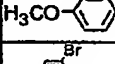
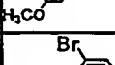
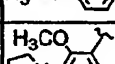
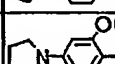
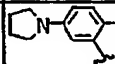
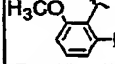
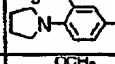
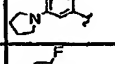
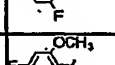
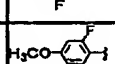
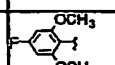
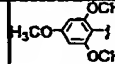
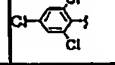
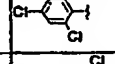
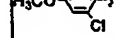


No.	R1	R2	R3	R4
A0295	CH3-		H	H
A0296	CH3-		H	H
A0297	CH3-		H	H
A0298	CH3-		H	H
A0299	CH3-		H	H
A0300	CH3-		H	H
A0301	CH3-		H	H
A0302	CH3-		H	H
A0303	CH3-		H	H
A0304	CH3-		H	H
A0305	CH3-		H	H
A0306	CH3-		H	H
A0307	CH3-		H	H
A0308	CH3-		H	H
A0309	CH3-		H	H
A0310	CH3-		H	H
A0311	CH3-		H	H
A0312	CH3-		H	H
A0313	CH3-		H	H
A0314	CH3-		H	H
A0315	CH3-		H	H

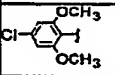
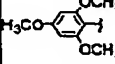
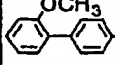
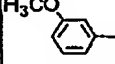
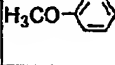
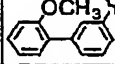
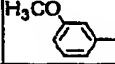
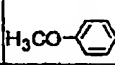
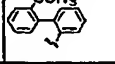
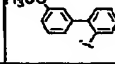
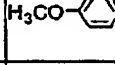
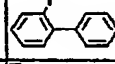
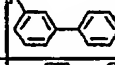

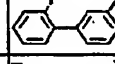
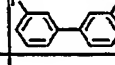
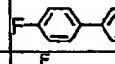
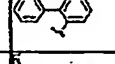
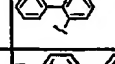

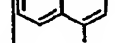
No.	R1	R2	R3	R4
A0316	CH3-		H	H
A0317	CH3-		H	H
A0318	CH3-		H	H
A0319	CH3-		H	H
A0320	CH3-		H	H
A0321	CH3-		H	H
A0322	CH3-		H	H
A0323	CH3-		H	H
A0324	CH3-		H	H
A0325	CH3-		H	H
A0326	CH3-		H	H
A0327	CH3-		H	H
A0328	CH3-		H	H
A0329	CH3-		H	H
A0330	CH3-		H	H
A0331	CH3-		H	H
A0332	CH3-		H	H
A0333	CH3-		H	H
A0334	CH3-		H	H
A0335	CH3-		H	H
A0336	CH3-		H	H

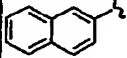




















No.	R1	R2	R3	R4
A0337	CH3-		H	H
A0338	CH3-		H	H
A0339	CH3-		H	H
A0340	CH3-		H	H
A0341	CH3-		H	H
A0342	CH3-		H	H
A0343	CH3-		H	H
A0344	CH3-		H	H
A0345	CH3-		H	H
A0346	CH3-		H	H
A0347	CH3-		H	H
A0348	CH3-		H	H
A0349	CH3-		H	H
A0350	CH3-		H	H
A0351	CH3-		H	H
A0352	CH3-		H	H
A0353	CH3-		H	H
A0354	CH3-		H	H
A0355	CH3-		H	H
A0356	CH3-		H	H
A0357	CH3-		H	H






















No.	R1	R2	R3	R4
A0358	CH3-		H	H
A0359	CH3-		H	H
A0360	CH3-		H	H
A0361	CH3-		H	H
A0362	CH3-		H	H
A0363	CH3-		H	H
A0364	CH3-		H	H
A0365	CH3-		H	H
A0366	CH3-		H	H
A0367	CH3-		H	H
A0368	CH3-		H	H
A0369	CH3-		H	H
A0370	CH3-		H	H
A0371	CH3-		H	H
A0372	CH3-		H	H
A0373	CH3-		H	H
A0374	CH3-		H	H
A0375	CH3-		H	H
A0376	CH3-		H	H
A0377	CH3-		H	H
A0378	CH3-		H	H






















No.	R1	R2	R3	R4
A0379	CH3-		H	H
A0380	CH3-		H	H
A0381	CH3-		H	H
A0382	CH3-		H	H
A0383	CH3-		H	H
A0384	CH3-		H	H
A0385	CH3-		H	H
A0386	CH3-		H	H
A0387	CH3-		H	H
A0388	CH3-		H	H
A0389	CH3-		H	H
A0390	CH3-		H	H
A0391	CH3-		H	H
A0392	CH3-		H	H
A0393	CH3-		H	H
A0394	CH3-		H	H
A0395	CH3-		H	H
A0396	CH3-		H	H
A0397	CH3-		H	H
A0398	CH3-		H	H
A0399	CH3-		H	H

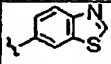
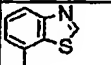
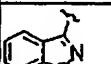
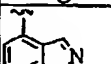
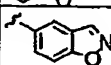
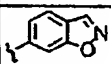
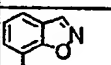
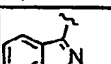
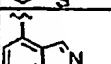
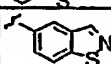
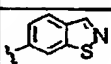
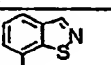
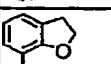
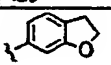
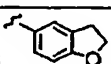
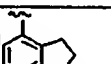

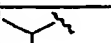

No.	R1	R2	R3	R4
A0400	CH3-		H	H
A0401	CH3-		H	H
A0402	CH3-		H	H
A0403	CH3-		H	H
A0404	CH3-		H	H
A0405	CH3-		H	H
A0406	CH3-		H	H
A0407	CH3-		H	H
A0408	CH3-		H	H
A0409	CH3-		H	H
A0410	CH3-		H	H
A0411	CH3-		H	H
A0412	CH3-		H	H
A0413	CH3-		H	H
A0414	CH3-		H	H
A0415	CH3-		H	H
A0416	CH3-		H	H
A0417	CH3-		H	H
A0418	CH3-		H	H
A0419	CH3-		H	H
A0420	CH3-		H	H




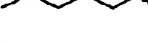
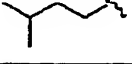



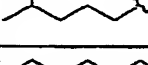

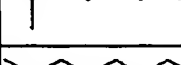

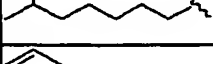
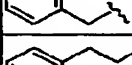

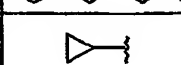





No.	R1	R2	R3	R4
A0421	CH3-		H	H
A0422	CH3-		H	H
A0423	CH3-		H	H
A0424	CH3-		H	H
A0425	CH3-		H	H
A0426	CH3-		H	H
A0427	CH3-		H	H
A0428	CH3-		H	H
A0429	CH3-		H	H
A0430	CH3-		H	H
A0431	CH3-		H	H
A0432	CH3-		H	H
A0433	CH3-		H	H
A0434	CH3-		H	H
A0435	CH3-		H	H
A0436	CH3-		H	H
A0437	CH3-		H	H
A0438	CH3-		H	H
A0439	CH3-		H	H
A0440	CH3-		H	H
A0441	CH3-		H	H






















No.	R1	R2	R3	R4
A0442	CH3-		H	H
A0443	CH3-		H	H
A0444	CH3-		H	H
A0445	CH3-		H	H
A0446	CH3-		H	H
A0447	CH3-		H	H
A0448	CH3-		H	H
A0449	CH3-		H	H
A0450	CH3-		H	H
A0451	CH3-		H	H
A0452	CH3-		H	H
A0453	CH3-		H	H
A0454	CH3-		H	H
A0455	CH3-		H	H
A0456	CH3-		H	H
A0457	CH3-		H	H
A0458	CH3-		H	H
A0459	CH3-		H	H
A0460	CH3-		H	H
A0461	CH3-		H	H
A0462	CH3-		H	H

No.	R1	R2	R3	R4
A0463	CH3-		H	H
A0464	CH3-		H	H
A0465	CH3-		H	H
A0466	CH3-		H	H
A0467	CH3-		H	H
A0468	CH3-		H	H
A0469	CH3-		H	H
A0470	CH3-		H	H
A0471	CH3-		H	H
A0472	CH3-		H	H
A0473	CH3-		H	H
A0474	CH3-		H	H
A0475	CH3-		H	H
A0476	CH3-		H	H
A0477	CH3-		H	H
A0478	CH3-		H	H
A0479	CH3-		H	H
A0480	CH3-		H	H
A0481	CH3-		H	H
A0482	CH3-		H	H
A0483	CH3-		H	H

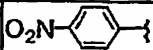

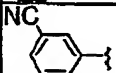
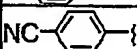

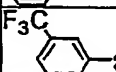

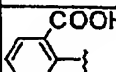
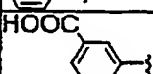
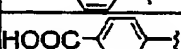
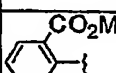
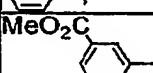
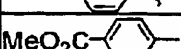
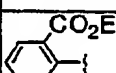
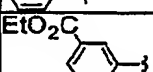
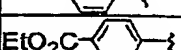
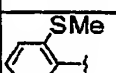

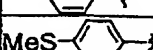
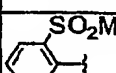
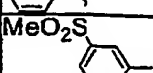
No.	R1	R2	R3	R4
A0484	CH3-		H	H
A0485	CH3-		H	H
A0486	CH3-		H	H
A0487	CH3-		H	H
A0488	CH3-		H	H
A0489	CH3-		H	H
A0490	CH3-		H	H
A0491	CH3-		H	H
A0492	CH3-		H	H
A0493	CH3-		H	H
A0494	CH3-		H	H
A0495	CH3-		H	H
A0496	CH3-		H	H
A0497	CH3-		H	H
A0498	CH3-		H	H
A0499	CH3-		H	H
A0500	CH3-		H	H
A0501	CH3-		H	H
A0502	CH3-		H	H
A0503	CH3-		H	H
A0504	CH3-		H	H

No.	R1	R2	R3	R4
A0505	CH3-		H	H
A0506	CH3-		H	H
A0507	CH3-		H	H
A0508	CH3-		H	H
A0509	CH3-		H	H
A0510	CH3-		H	H
A0511	CH3-		H	H
A0512	CH3-		H	H
A0513	CH3-		H	H
A0514	CH3-		H	H
A0515	CH3-		H	H
A0516	CH3-		H	H
A0517	CH3-		H	H
A0518	CH3-		H	H
A0519	CH3-		H	H
A0520	CH3-		H	H
A0521	CH3-	CH3-	H	CH3
A0522	CH3-	CH3CH2-	H	CH3
A0523	CH3-		H	CH3
A0524	CH3-		H	CH3
A0525	CH3-		H	CH3



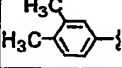


















No.	R1	R2	R3	R4
A0526	CH3-		H	CH3
A0527	CH3-		H	CH3
A0528	CH3-		H	CH3
A0529	CH3-		H	CH3
A0530	CH3-		H	CH3
A0531	CH3-		H	CH3
A0532	CH3-		H	CH3
A0533	CH3-		H	CH3
A0534	CH3-		H	CH3
A0535	CH3-		H	CH3
A0536	CH3-		H	CH3
A0537	CH3-		H	CH3
A0538	CH3-		H	CH3
A0539	CH3-		H	CH3
A0540	CH3-		H	CH3
A0541	CH3-		H	CH3
A0542	CH3-		H	CH3
A0543	CH3-		H	CH3
A0544	CH3-		H	CH3
A0545	CH3-		H	CH3
A0546	CH3-		H	CH3






















No.	R1	R2	R3	R4
A0547	CH3-		H	CH3
A0548	CH3-		H	CH3
A0549	CH3-		H	CH3
A0550	CH3-		H	CH3
A0551	CH3-		H	CH3
A0552	CH3-		H	CH3
A0553	CH3-		H	CH3
A0554	CH3-		H	CH3
A0555	CH3-		H	CH3
A0556	CH3-		H	CH3
A0557	CH3-		H	CH3
A0558	CH3-		H	CH3
A0559	CH3-		H	CH3
A0560	CH3-		H	CH3
A0561	CH3-		H	CH3
A0562	CH3-		H	CH3
A0563	CH3-		H	CH3
A0564	CH3-		H	CH3
A0565	CH3-		H	CH3
A0566	CH3-		H	CH3
A0567	CH3-		H	CH3

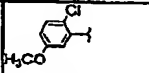
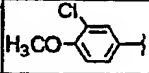
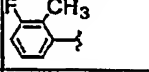
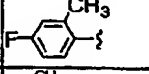
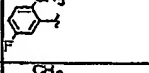
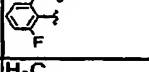
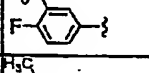
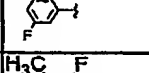
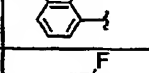
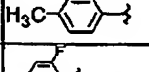
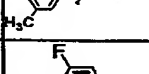
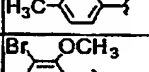
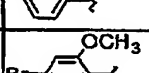
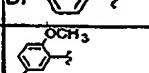
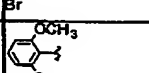
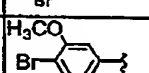
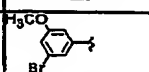
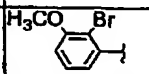
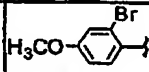
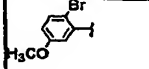

No.	R1	R2	R3	R4
A0568	CH ₃ -		H	CH ₃
A0569	CH ₃ -		H	CH ₃
A0570	CH ₃ -		H	CH ₃
A0571	CH ₃ -		H	CH ₃
A0572	CH ₃ -		H	CH ₃
A0573	CH ₃ -		H	CH ₃
A0574	CH ₃ -		H	CH ₃
A0575	CH ₃ -		H	CH ₃
A0576	CH ₃ -		H	CH ₃
A0577	CH ₃ -		H	CH ₃
A0578	CH ₃ -		H	CH ₃
A0579	CH ₃ -		H	CH ₃
A0580	CH ₃ -		H	CH ₃
A0581	CH ₃ -		H	CH ₃
A0582	CH ₃ -		H	CH ₃
A0583	CH ₃ -		H	CH ₃
A0584	CH ₃ -		H	CH ₃
A0585	CH ₃ -		H	CH ₃
A0586	CH ₃ -		H	CH ₃
A0587	CH ₃ -		H	CH ₃
A0588	CH ₃ -		H	CH ₃

No.	R1	R2	R3	R4
A0589	CH3-		H	CH3
A0590	CH3-		H	CH3
A0591	CH3-		H	CH3
A0592	CH3-		H	CH3
A0593	CH3-		H	CH3
A0594	CH3-		H	CH3
A0595	CH3-		H	CH3
A0596	CH3-		H	CH3
A0597	CH3-		H	CH3
A0598	CH3-		H	CH3
A0599	CH3-		H	CH3
A0600	CH3-		H	CH3
A0601	CH3-		H	CH3
A0602	CH3-		H	CH3
A0603	CH3-		H	CH3
A0604	CH3-		H	CH3
A0605	CH3-		H	CH3
A0606	CH3-		H	CH3
A0607	CH3-		H	CH3
A0608	CH3-		H	CH3
A0609	CH3-		H	CH3

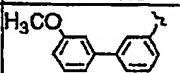
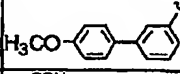

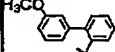
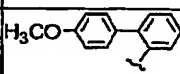
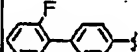

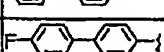
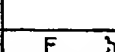
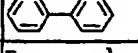
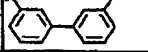


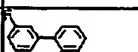

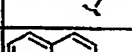
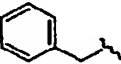
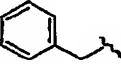

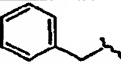

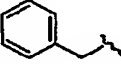
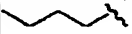
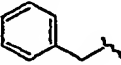
No.	R1	R2	R3	R4
A0610	CH3-		H	CH3
A0611	CH3-		H	CH3
A0612	CH3-		H	CH3
A0613	CH3-		H	CH3
A0614	CH3-		H	CH3
A0615	CH3-		H	CH3
A0616	CH3-		H	CH3
A0617	CH3-		H	CH3
A0618	CH3-		H	CH3
A0619	CH3-		H	CH3
A0620	CH3-		H	CH3
A0621	CH3-		H	CH3
A0622	CH3-		H	CH3
A0623	CH3-		H	CH3
A0624	CH3-		H	CH3
A0625	CH3-		H	CH3
A0626	CH3-		H	CH3
A0627	CH3-		H	CH3
A0628	CH3-		H	CH3
A0629	CH3-		H	CH3
A0630	CH3-		H	CH3




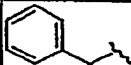

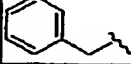



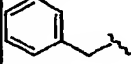

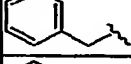

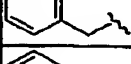
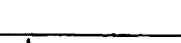

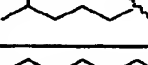
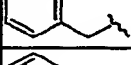



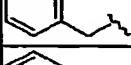


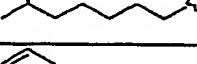
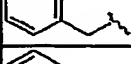
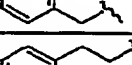
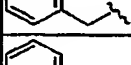


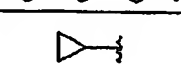
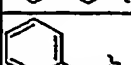

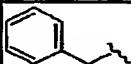

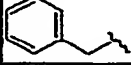

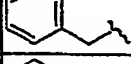

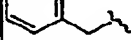


No.	R1	R2	R3	R4
A0631	CH3-		H	CH3
A0632	CH3-		H	CH3
A0633	CH3-		H	CH3
A0634	CH3-		H	CH3
A0635	CH3-		H	CH3
A0636	CH3-		H	CH3
A0637	CH3-		H	CH3
A0638	CH3-		H	CH3
A0639	CH3-		H	CH3
A0640	CH3-		H	CH3
A0641	CH3-		H	CH3
A0642	CH3-		H	CH3
A0643	CH3-		H	CH3
A0644	CH3-		H	CH3
A0645	CH3-		H	CH3
A0646	CH3-		H	CH3
A0647	CH3-		H	CH3
A0648	CH3-		H	CH3
A0649	CH3-		H	CH3
A0650	CH3-		H	CH3
A0651	CH3-		H	CH3


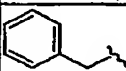

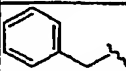

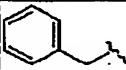

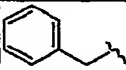

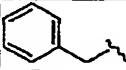

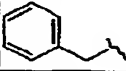

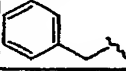

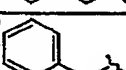

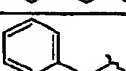

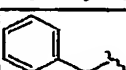

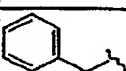

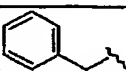

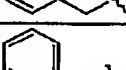

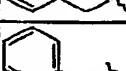



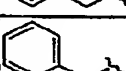

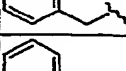

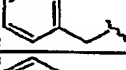

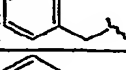

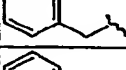

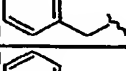
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A0655	CH3-		H	CH3
A0656	CH3-		H	CH3
A0657	CH3-		H	CH3
A0658	CH3-		H	CH3
A0659	CH3-		H	CH3
A0660	CH3-		H	CH3
A0661	CH3-		H	CH3
A0662	CH3-		H	CH3
A0663	CH3-		H	CH3
A0664	CH3-		H	CH3
A0665	CH3-		H	CH3
A0666	CH3-		H	CH3
A0667	CH3-		H	CH3
A0668	CH3-		H	CH3
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A0670	CH3-		H	CH3
A0671	CH3-		H	CH3
A0672	CH3-		H	CH3

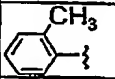
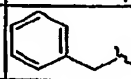
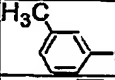
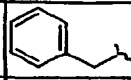
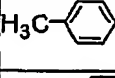
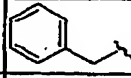
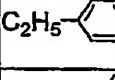
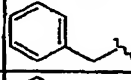
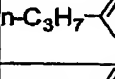
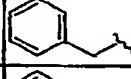
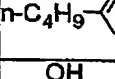
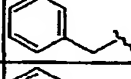
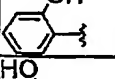
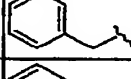
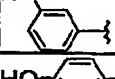
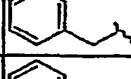
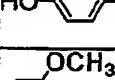
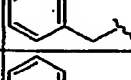
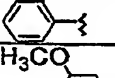
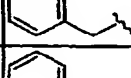
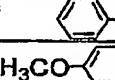
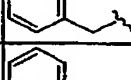
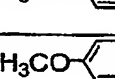
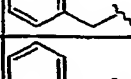
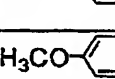
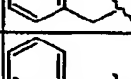
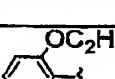
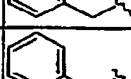
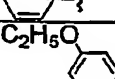
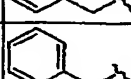
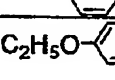
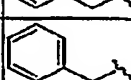
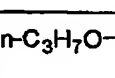
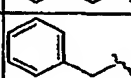
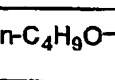
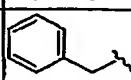
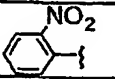
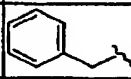
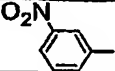
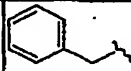


No.	R1	R2	R3	R4
A0673	CH3-		H	CH3
A0674	CH3-		H	CH3
A0675	CH3-		H	CH3
A0676	CH3-		H	CH3
A0677	CH3-		H	CH3
A0678	CH3-		H	CH3
A0679	CH3-		H	CH3
A0680	CH3-		H	CH3
A0681	CH3-		H	CH3
A0682	CH3-		H	CH3
A0683	CH3-		H	CH3
A0684	CH3-		H	CH3
A0685	CH3-		H	CH3
A0686	CH3-		H	CH3
A0687	CH3-		H	CH3
A0688	CH3-		H	CH3
A0689	CH3-		H	CH3
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A0693	CH3-		H	CH3

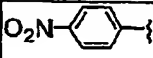
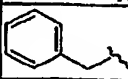

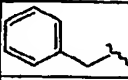
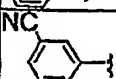
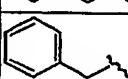
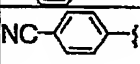
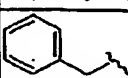

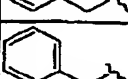
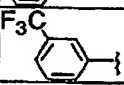
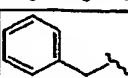
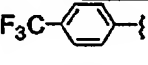
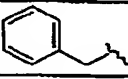

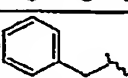
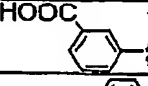
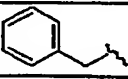
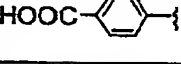
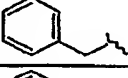
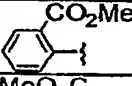
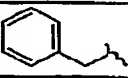
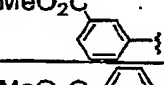
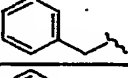
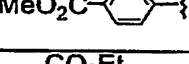
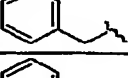
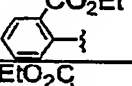
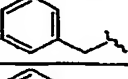
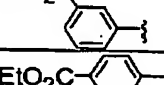
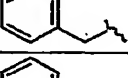
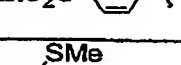
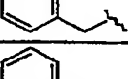
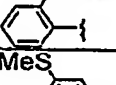
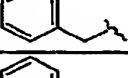
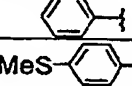
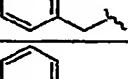
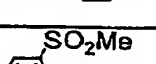
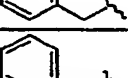
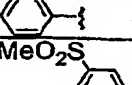
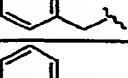
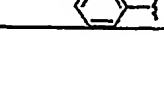
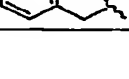
No.	R1	R2	R3	R4
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A0695	CH3-		H	CH3
A0696	CH3-		H	CH3
A0697	CH3-		H	CH3
A0698	CH3-		H	CH3
A0699	CH3-		H	CH3
A0700	CH3-		H	CH3
A0701	CH3-		H	CH3
A0702	CH3-		H	CH3
A0703	CH3-		H	CH3
A0704	CH3-		H	CH3
A0705	CH3-		H	CH3
A0706	CH3-		H	CH3
A0707	CH3-		H	CH3
A0708	CH3-		H	CH3
A0709	CH3-		H	CH3
A0710	CH3-		H	CH3
A0711	CH3-		H	CH3
A0712	CH3-		H	CH3
A0713	CH3-		H	CH3
A0714	CH3-		H	CH3

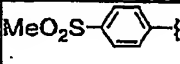
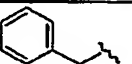

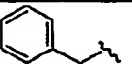
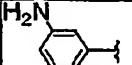
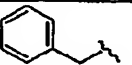
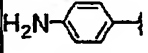
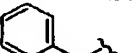
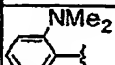

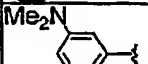
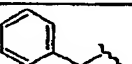
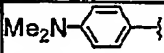

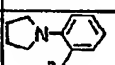
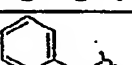
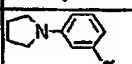
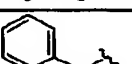
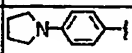

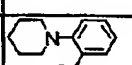

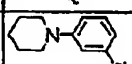
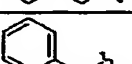
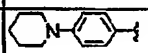

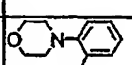

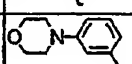

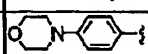

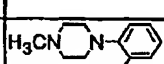

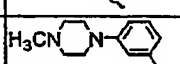

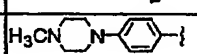

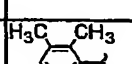

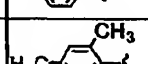

No.	R1	R2	R3	R4
A0715	CH3-		H	CH3
A0716	CH3-		H	CH3
A0717	CH3-		H	CH3
A0718	CH3-		H	CH3
A0719	CH3-		H	CH3
A0720	CH3-		H	CH3
A0721	CH3-		H	CH3
A0722	CH3-		H	CH3
A0723	CH3-		H	CH3
A0724	CH3-		H	CH3
A0725	CH3-		H	CH3
A0726	CH3-		H	CH3
A0727	CH3-		H	CH3
A0728	CH3-		H	CH3
A0729	CH3-		H	CH3
A0730	CH3-		H	CH3
A0731	CH3-	CH3-	H	
A0732	CH3-	CH3CH2-	H	
A0733	CH3-		H	
A0734	CH3-		H	
A0735	CH3-		H	


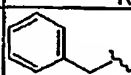

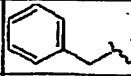
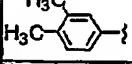
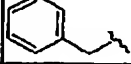

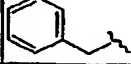

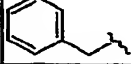
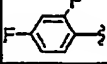
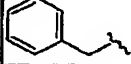

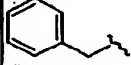

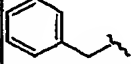
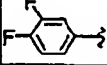
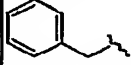

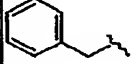

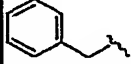
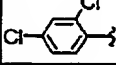
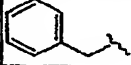

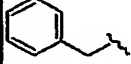

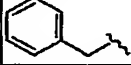
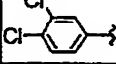
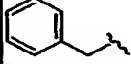

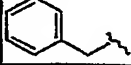
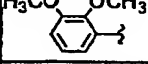
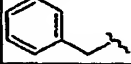
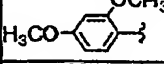
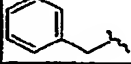
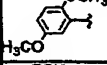
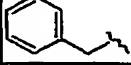
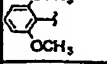
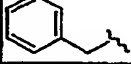
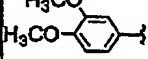
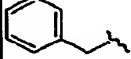
No.	R1	R2	R3	R4
A0736	CH3-		H	
A0737	CH3-		H	
A0738	CH3-		H	
A0739	CH3-		H	
A0740	CH3-		H	
A0741	CH3-		H	
A0742	CH3-		H	
A0743	CH3-		H	
A0744	CH3-		H	
A0745	CH3-		H	
A0746	CH3-		H	
A0747	CH3-		H	
A0748	CH3-		H	
A0749	CH3-		H	
A0750	CH3-		H	
A0751	CH3-		H	
A0752	CH3-		H	
A0753	CH3-		H	
A0754	CH3-		H	
A0755	CH3-		H	
A0756	CH3-		H	

No.	R1	R2	R3	R4
A0757	CH3-		H	
A0758	CH3-		H	
A0759	CH3-		H	
A0760	CH3-		H	
A0761	CH3-		H	
A0762	CH3-		H	
A0763	CH3-		H	
A0764	CH3-		H	
A0765	CH3-		H	
A0766	CH3-		H	
A0767	CH3-		H	
A0768	CH3-		H	
A0769	CH3-		H	
A0770	CH3-		H	
A0771	CH3-		H	
A0772	CH3-		H	
A0773	CH3-		H	
A0774	CH3-		H	
A0775	CH3-		H	
A0776	CH3-		H	
A0777	CH3-		H	

No.	R1	R2	R3	R4
A0778	CH ₃ -		H	
A0779	CH ₃ -		H	
A0780	CH ₃ -		H	
A0781	CH ₃ -		H	
A0782	CH ₃ -		H	
A0783	CH ₃ -		H	
A0784	CH ₃ -		H	
A0785	CH ₃ -		H	
A0786	CH ₃ -		H	
A0787	CH ₃ -		H	
A0788	CH ₃ -		H	
A0789	CH ₃ -		H	
A0790	CH ₃ -		H	
A0791	CH ₃ -		H	
A0792	CH ₃ -		H	
A0793	CH ₃ -		H	
A0794	CH ₃ -		H	
A0795	CH ₃ -		H	
A0796	CH ₃ -		H	
A0797	CH ₃ -		H	
A0798	CH ₃ -		H	

No.	R1	R2	R3	R4
A0799	CH ₃ -		H	
A0800	CH ₃ -		H	
A0801	CH ₃ -		H	
A0802	CH ₃ -		H	
A0803	CH ₃ -		H	
A0804	CH ₃ -		H	
A0805	CH ₃ -		H	
A0806	CH ₃ -		H	
A0807	CH ₃ -		H	
A0808	CH ₃ -		H	
A0809	CH ₃ -		H	
A0810	CH ₃ -		H	
A0811	CH ₃ -		H	
A0812	CH ₃ -		H	
A0813	CH ₃ -		H	
A0814	CH ₃ -		H	
A0815	CH ₃ -		H	
A0816	CH ₃ -		H	
A0817	CH ₃ -		H	
A0818	CH ₃ -		H	
A0819	CH ₃ -		H	

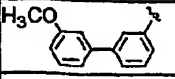
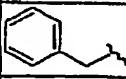
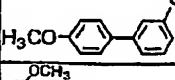
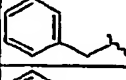
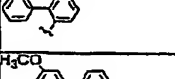
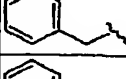
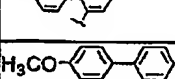
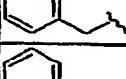
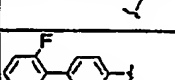
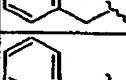
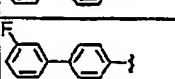
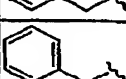
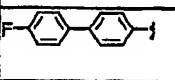
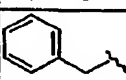
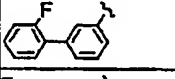
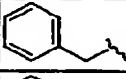
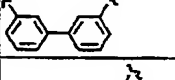
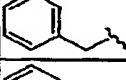
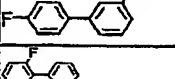
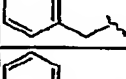
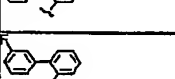
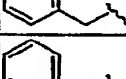
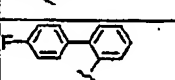
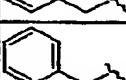
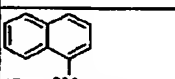
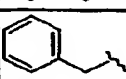
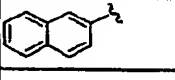
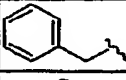
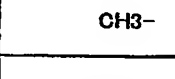
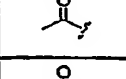
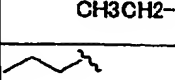
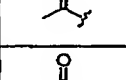
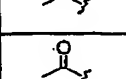
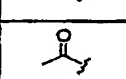
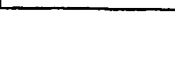





No.	R1	R2	R3	R4
A0820	CH ₃ -	MeO ₂ S- 	H	
A0821	CH ₃ -		H	
A0822	CH ₃ -		H	
A0823	CH ₃ -		H	
A0824	CH ₃ -		H	
A0825	CH ₃ -		H	
A0826	CH ₃ -		H	
A0827	CH ₃ -		H	
A0828	CH ₃ -		H	
A0829	CH ₃ -		H	
A0830	CH ₃ -		H	
A0831	CH ₃ -		H	
A0832	CH ₃ -		H	
A0833	CH ₃ -		H	
A0834	CH ₃ -		H	
A0835	CH ₃ -		H	
A0836	CH ₃ -		H	
A0837	CH ₃ -		H	
A0838	CH ₃ -		H	
A0839	CH ₃ -		H	
A0840	CH ₃ -		H	







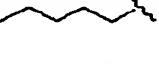

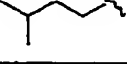







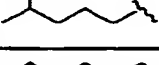

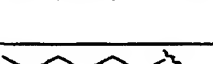



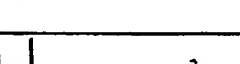



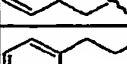











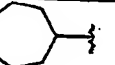



No.	R1	R2	R3	R4
A0841	CH3-		H	
A0842	CH3-		H	
A0843	CH3-		H	
A0844	CH3-		H	
A0845	CH3-		H	
A0846	CH3-		H	
A0847	CH3-		H	
A0848	CH3-		H	
A0849	CH3-		H	
A0850	CH3-		H	
A0851	CH3-		H	
A0852	CH3-		H	
A0853	CH3-		H	
A0854	CH3-		H	
A0855	CH3-		H	
A0856	CH3-		H	
A0857	CH3-		H	
A0858	CH3-		H	
A0859	CH3-		H	
A0860	CH3-		H	
A0861	CH3-		H	











































No.	R1	R2	R3	R4
A0862	CH3-		H	
A0863	CH3-		H	
A0864	CH3-		H	
A0865	CH3-		H	
A0866	CH3-		H	
A0867	CH3-		H	
A0868	CH3-		H	
A0869	CH3-		H	
A0870	CH3-		H	
A0871	CH3-		H	
A0872	CH3-		H	
A0873	CH3-		H	
A0874	CH3-		H	
A0875	CH3-		H	
A0876	CH3-		H	
A0877	CH3-		H	
A0878	CH3-		H	
A0879	CH3-		H	
A0880	CH3-		H	
A0881	CH3-		H	
A0882	CH3-		H	

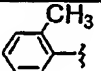

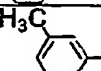

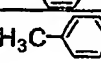

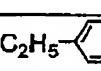

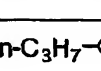

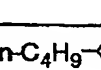

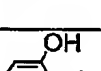

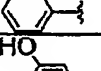

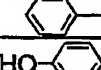

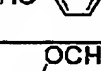

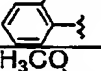

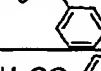

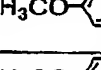

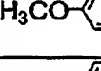

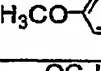

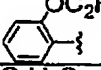

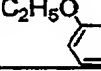

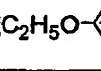

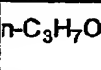

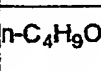

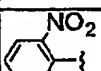

No.	R1	R2	R3	R4
A0883	CH3-		H	
A0884	CH3-		H	
A0885	CH3-		H	
A0886	CH3-		H	
A0887	CH3-		H	
A0888	CH3-		H	
A0889	CH3-		H	
A0890	CH3-		H	
A0891	CH3-		H	
A0892	CH3-		H	
A0893	CH3-		H	
A0894	CH3-		H	
A0895	CH3-		H	
A0896	CH3-		H	
A0897	CH3-		H	
A0898	CH3-		H	
A0899	CH3-		H	
A0900	CH3-		H	
A0901	CH3-		H	
A0902	CH3-		H	
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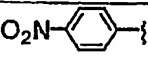



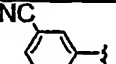

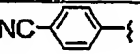



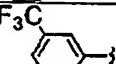

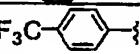



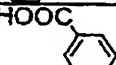

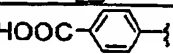

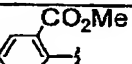

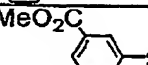

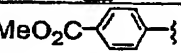



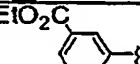

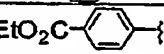



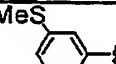

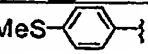

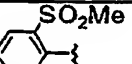

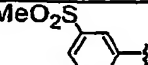

No.	R1	R2	R3	R4
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A0905	CH ₃ -		H	
A0906	CH ₃ -		H	
A0907	CH ₃ -		H	
A0908	CH ₃ -		H	
A0909	CH ₃ -		H	
A0910	CH ₃ -		H	
A0911	CH ₃ -		H	
A0912	CH ₃ -		H	
A0913	CH ₃ -		H	
A0914	CH ₃ -		H	
A0915	CH ₃ -		H	
A0916	CH ₃ -		H	
A0917	CH ₃ -		H	
A0918	CH ₃ -		H	
A0919	CH ₃ -		H	
A0920	CH ₃ -		H	
A0921	CH ₃ -		H	
A0922	CH ₃ -		H	
A0923	CH ₃ -		H	
A0924	CH ₃ -		H	

No.	R1	R2	R3	R4
A0925	CH ₃ -		H	
A0926	CH ₃ -		H	
A0927	CH ₃ -		H	
A0928	CH ₃ -		H	
A0929	CH ₃ -		H	
A0930	CH ₃ -		H	
A0931	CH ₃ -		H	
A0932	CH ₃ -		H	
A0933	CH ₃ -		H	
A0934	CH ₃ -		H	
A0935	CH ₃ -		H	
A0936	CH ₃ -		H	
A0937	CH ₃ -		H	
A0938	CH ₃ -		H	
A0939	CH ₃ -		H	
A0940	CH ₃ -		H	
A0941	CH ₃ -	CH ₃ -	H	
A0942	CH ₃ -	CH ₃ CH ₂ -	H	
A0943	CH ₃ -		H	
A0944	CH ₃ -		H	
A0945	CH ₃ -		H	





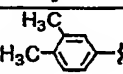

















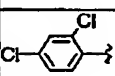





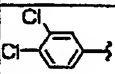



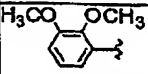

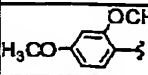

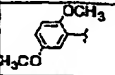

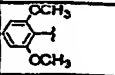

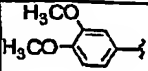

No.	R1	R2	R3	R4
A0946	CH3-		H	
A0947	CH3-		H	
A0948	CH3-		H	
A0949	CH3-		H	
A0950	CH3-		H	
A0951	CH3-		H	
A0952	CH3-		H	
A0953	CH3-		H	
A0954	CH3-		H	
A0955	CH3-		H	
A0956	CH3-		H	
A0957	CH3-		H	
A0958	CH3-		H	
A0959	CH3-		H	
A0960	CH3-		H	
A0961	CH3-		H	
A0962	CH3-		H	
A0963	CH3-		H	
A0964	CH3-		H	
A0965	CH3-		H	
A0966	CH3-		H	

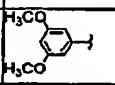

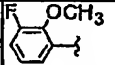

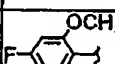

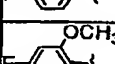

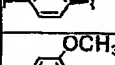

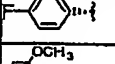

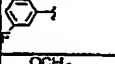

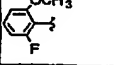

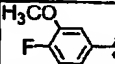

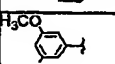

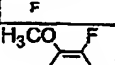

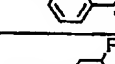

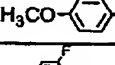

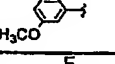

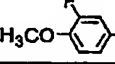

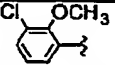

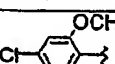

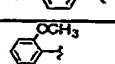

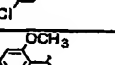

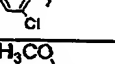

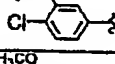

No.	R1	R2	R3	R4
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A0968	CH3-		H	
A0969	CH3-		H	
A0970	CH3-		H	
A0971	CH3-		H	
A0972	CH3-		H	
A0973	CH3-		H	
A0974	CH3-		H	
A0975	CH3-		H	
A0976	CH3-		H	
A0977	CH3-		H	
A0978	CH3-		H	
A0979	CH3-		H	
A0980	CH3-		H	
A0981	CH3-		H	
A0982	CH3-		H	
A0983	CH3-		H	
A0984	CH3-		H	
A0985	CH3-		H	
A0986	CH3-		H	
A0987	CH3-		H	

No.	R1	R2	R3	R4
A0988	CH3-		H	
A0989	CH3-		H	
A0990	CH3-		H	
A0991	CH3-		H	
A0992	CH3-		H	
A0993	CH3-		H	
A0994	CH3-		H	
A0995	CH3-		H	
A0996	CH3-		H	
A0997	CH3-		H	
A0998	CH3-		H	
A0999	CH3-		H	
A1000	CH3-		H	
A1001	CH3-		H	
A1002	CH3-		H	
A1003	CH3-		H	
A1004	CH3-		H	
A1005	CH3-		H	
A1006	CH3-		H	
A1007	CH3-		H	
A1008	CH3-		H	

No.	R1	R2	R3	R4
A1009	CH ₃ -		H	
A1010	CH ₃ -		H	
A1011	CH ₃ -		H	
A1012	CH ₃ -		H	
A1013	CH ₃ -		H	
A1014	CH ₃ -		H	
A1015	CH ₃ -		H	
A1016	CH ₃ -		H	
A1017	CH ₃ -		H	
A1018	CH ₃ -		H	
A1019	CH ₃ -		H	
A1020	CH ₃ -		H	
A1021	CH ₃ -		H	
A1022	CH ₃ -		H	
A1023	CH ₃ -		H	
A1024	CH ₃ -		H	
A1025	CH ₃ -		H	
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A1028	CH ₃ -		H	
A1029	CH ₃ -		H	

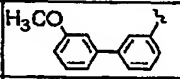

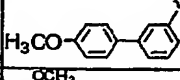

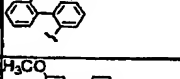

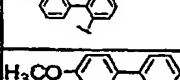

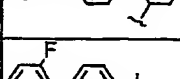

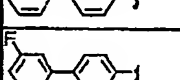

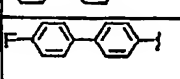

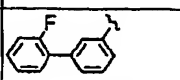

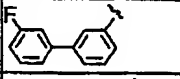

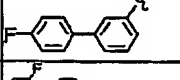

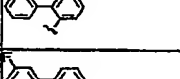

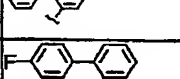

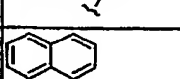

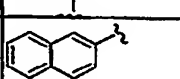

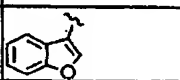

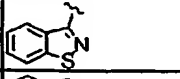



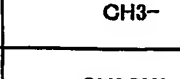

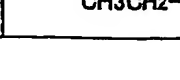

No.	R1	R2	R3	R4
A1030	CH3-		H	
A1031	CH3-		H	
A1032	CH3-		H	
A1033	CH3-		H	
A1034	CH3-		H	
A1035	CH3-		H	
A1036	CH3-		H	
A1037	CH3-		H	
A1038	CH3-		H	
A1039	CH3-		H	
A1040	CH3-		H	
A1041	CH3-		H	
A1042	CH3-		H	
A1043	CH3-		H	
A1044	CH3-		H	
A1045	CH3-		H	
A1046	CH3-		H	
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A1050	CH3-		H	




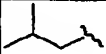




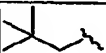


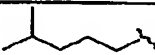

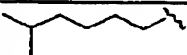

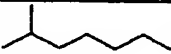
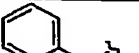
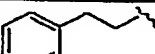



No.	R1	R2	R3	R4
A1051	CH3-		H	
A1052	CH3-		H	
A1053	CH3-		H	
A1054	CH3-		H	
A1055	CH3-		H	
A1056	CH3-		H	
A1057	CH3-		H	
A1058	CH3-		H	
A1059	CH3-		H	
A1060	CH3-		H	
A1061	CH3-		H	
A1062	CH3-		H	
A1063	CH3-		H	
A1064	CH3-		H	
A1065	CH3-		H	
A1066	CH3-		H	
A1067	CH3-		H	
A1068	CH3-		H	
A1069	CH3-		H	
A1070	CH3-		H	
A1071	CH3-		H	



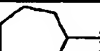


















No.	R1	R2	R3	R4
A1072	CH3-		H	
A1073	CH3-		H	
A1074	CH3-		H	
A1075	CH3-		H	
A1076	CH3-		H	
A1077	CH3-		H	
A1078	CH3-		H	
A1079	CH3-		H	
A1080	CH3-		H	
A1081	CH3-		H	
A1082	CH3-		H	
A1083	CH3-		H	
A1084	CH3-		H	
A1085	CH3-		H	
A1086	CH3-		H	
A1087	CH3-		H	
A1088	CH3-		H	
A1089	CH3-		H	
A1090	CH3-		H	
A1091	CH3-		H	
A1092	CH3-		H	






















No.	R1	R2	R3	R4
A1093	CH3-		H	
A1094	CH3-		H	
A1095	CH3-		H	
A1096	CH3-		H	
A1097	CH3-		H	
A1098	CH3-		H	
A1099	CH3-		H	
A1100	CH3-		H	
A1101	CH3-		H	
A1102	CH3-		H	
A1103	CH3-		H	
A1104	CH3-		H	
A1105	CH3-		H	
A1106	CH3-		H	
A1107	CH3-		H	
A1108	CH3-		H	
A1109	CH3-		H	
A1110	CH3-		H	
A1111	CH3-		H	
A1112	CH3-		H	
A1113	CH3-		H	

No.	R1	R2	R3	R4
A1114	CH3-		H	
A1115	CH3-		H	
A1116	CH3-		H	
A1117	CH3-		H	
A1118	CH3-		H	
A1119	CH3-		H	
A1120	CH3-		H	
A1121	CH3-		H	
A1122	CH3-		H	
A1123	CH3-		H	
A1124	CH3-		H	
A1125	CH3-		H	
A1126	CH3-		H	
A1127	CH3-		H	
A1128	CH3-		H	
A1129	CH3-		H	
A1130	CH3-		H	
A1131	CH3-		H	
A1132	CH3-		H	
A1133	CH3-		H	
A1134	CH3-		H	

No.	R1	R2	R3	R4
A1135	CH3-		H	
A1136	CH3-		H	
A1137	CH3-		H	
A1138	CH3-		H	
A1139	CH3-		H	
A1140	CH3-		H	
A1141	CH3-		H	
A1142	CH3-		H	
A1143	CH3-		H	
A1144	CH3-		H	
A1145	CH3-		H	
A1146	CH3-		H	
A1147	CH3-		H	
A1148	CH3-		H	
A1149	CH3-		H	
A1150	CH3-		H	
A1151	CH3-		H	
A1152	CH3-		H	
A1153	CH3-		H	
A1154	CH3-	CH3-	CH3-	H
A1155	CH3-	CH3CH2-	CH3-	H








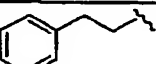
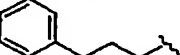




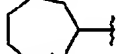





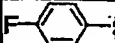
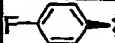
No.	R1	R2	R3	R4
A1156	CH3-		CH3-	H
A1157	CH3-		CH3-	H
A1158	CH3-		CH3-	H
A1159	CH3-		CH3-	H
A1160	CH3-		CH3-	H
A1161	CH3-		CH3-	H
A1162	CH3-		CH3-	H
A1163	CH3-		CH3-	H
A1164	CH3-		CH3-	H
A1165	CH3-		CH3-	H
A1166	CH3-		CH3-	H
A1167	CH3-		CH3-	H
A1168	CH3-		CH3-	H
A1169	CH3-		CH3-	H
A1170	CH3-		CH3-	H
A1171	CH3-		CH3-	H
A1172	CH3-		CH3-	H
A1173	CH3-		CH3-	H
A1174	CH3-		CH3-	H
A1175	CH3-		CH3-	H
A1176	CH3-		CH3-	H

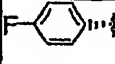
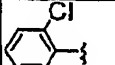
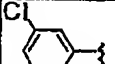
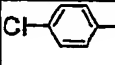
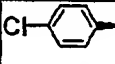
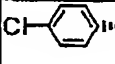
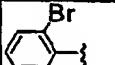
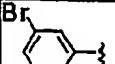
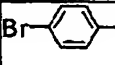
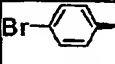
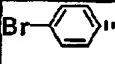
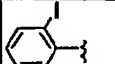
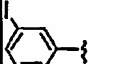
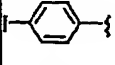
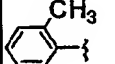
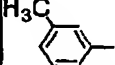
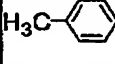
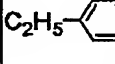
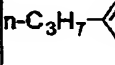
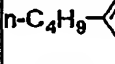
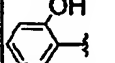
No.	R1	R2	R3	R4
A1177	CH3-		CH3-	H
A1178	CH3-		CH3-	H
A1179	CH3-		CH3-	H
A1180	CH3-		CH3-	H
A1181	CH3-		CH3-	H
A1182	CH3-		CH3-	H
A1183	CH3-		CH3-	H
A1184	CH3-		CH3-	H
A1185	CH3-		CH3-	H
A1186	CH3-		CH3-	H
A1187	CH3-		CH3-	H
A1188	CH3-		CH3-	H
A1189	CH3-		CH3-	H
A1190	CH3-		CH3-	H
A1191	CH3-		CH3-	H
A1192	CH3-		CH3-	H
A1193	CH3-		CH3-	H
A1194	CH3-		CH3-	H
A1195	CH3-		CH3-	H
A1196	CH3-		CH3-	H
A1197	CH3-		CH3-	H

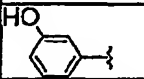
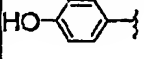
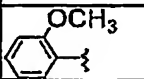
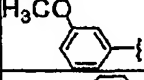
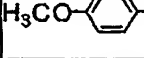
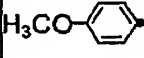
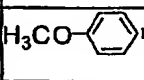
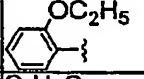
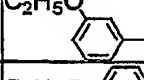
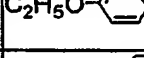
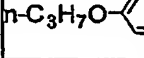
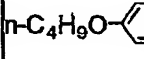
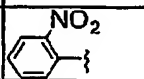
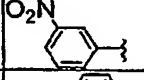
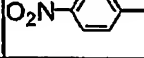
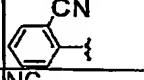
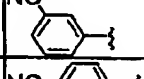

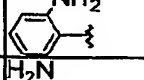
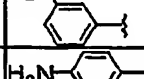

No.	R1	R2	R3	R4
A1198	CH3-		CH3-	H
A1199	CH3-		CH3-	H
A1200	CH3-		CH3-	H
A1201	CH3-		CH3-	H
A1202	CH3-		CH3-	H
A1203	CH3-		CH3-	H
A1204	CH3-		CH3-	H
A1205	CH3-		CH3-	H
A1206	CH3-		CH3-	H
A1207	CH3-		CH3-	H
A1208	CH3-		CH3-	H
A1209	CH3-		CH3-	H
A1210	CH3-		CH3-	H
A1211	CH3-		CH3-	H
A1212	CH3-		CH3-	H
A1213	CH3-		CH3-	H
A1214	CH3-		CH3-	H
A1215	CH3-		CH3-	H
A1216	CH3-		CH3-	H
A1217	CH3-		CH3-	H
A1218	CH3-		CH3-	H

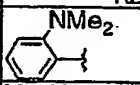
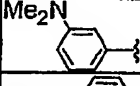
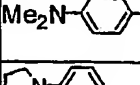
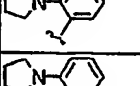
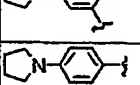
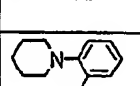
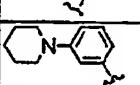
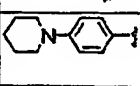
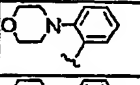
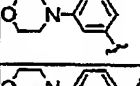
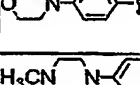
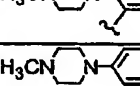
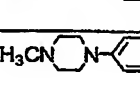
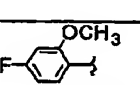
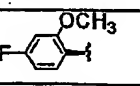
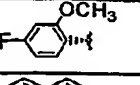
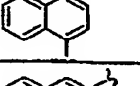
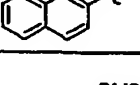
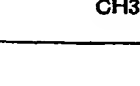

No.	R1	R2	R3	R4
A1219	CH ₃ -		CH ₃ -	H
A1220	CH ₃ -		CH ₃ -	H
A1221	CH ₃ -		CH ₃ -	H
A1222	CH ₃ -		CH ₃ -	H
A1223	CH ₃ -		CH ₃ -	H
A1224	CH ₃ -		CH ₃ -	H
A1225	CH ₃ -		CH ₃ -	H
A1226	CH ₃ -		CH ₃ -	H
A1227	CH ₃ -		CH ₃ -	H
A1228	CH ₃ -		CH ₃ -	H
A1229	CH ₃ -		CH ₃ -	H
A1230	CH ₃ -		CH ₃ -	H
A1231	CH ₃ -		CH ₃ -	H
A1232	CH ₃ -		CH ₃ -	H
A1233	CH ₃ -		CH ₃ -	H
A1234	CH ₃ -		CH ₃ -	H
A1235	CH ₃ -		CH ₃ -	H
A1236	CH ₃ -		CH ₃ -	H
A1237	CH ₃ -		CH ₃ -	H
A1238	CH ₃ -		CH ₃ -	H
A1239	CH ₃ -		CH ₃ -	H



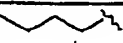
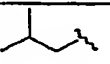
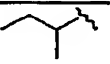


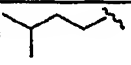
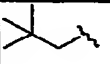
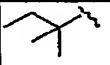

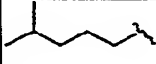
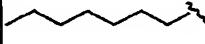
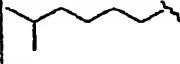
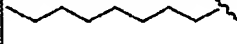
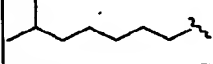
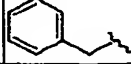
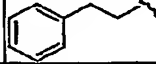
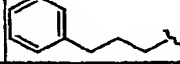

No.	R1	R2	R3	R4
A1240	CH3-		CH3-	H
A1241	CH3-		CH3-	H
A1242	CH3-		CH3-	H
A1243	CH3-		CH3-	H
A1244	CH3-		CH3-	H
A1245	CH3-		CH3-	H
A1246	CH3-		CH3-	H
A1247	CH3-		CH3-	H
A1248	CH3-		CH3-	H
A1249	CH3-	CH3-	H	CH3-
A1250	CH3-	CH3CH2-	H	CH3-
A1251	CH3-		H	CH3-
A1252	CH3-		H	CH3-
A1253	CH3-		H	CH3-
A1254	CH3-		H	CH3-
A1255	CH3-		H	CH3-
A1256	CH3-		H	CH3-
A1257	CH3-		H	CH3-
A1258	CH3-		H	CH3-
A1259	CH3-		H	CH3-
A1260	CH3-		H	CH3-



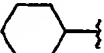
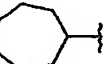

















No.	R1	R2	R3	R4
A1261	CH3-		H	CH3-
A1262	CH3-		H	CH3-
A1263	CH3-		H	CH3-
A1264	CH3-		H	CH3-
A1265	CH3-		H	CH3-
A1266	CH3-		H	CH3-
A1267	CH3-		H	CH3-
A1268	CH3-		H	CH3-
A1269	CH3-		H	CH3-
A1270	CH3-		H	CH3-
A1271	CH3-		H	CH3-
A1272	CH3-		H	CH3-
A1273	CH3-		H	CH3-
A1274	CH3-		H	CH3-
A1275	CH3-		H	CH3-
A1276	CH3-		H	CH3-
A1277	CH3-		H	CH3-
A1278	CH3-		H	CH3-
A1279	CH3-		H	CH3-
A1280	CH3-		H	CH3-
A1281	CH3-		H	CH3-

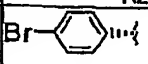




















No.	R1	R2	R3	R4
A1282	CH ₃ -		H	CH ₃ -
A1283	CH ₃ -		H	CH ₃ -
A1284	CH ₃ -		H	CH ₃ -
A1285	CH ₃ -		H	CH ₃ -
A1286	CH ₃ -		H	CH ₃ -
A1287	CH ₃ -		H	CH ₃ -
A1288	CH ₃ -		H	CH ₃ -
A1289	CH ₃ -		H	CH ₃ -
A1290	CH ₃ -		H	CH ₃ -
A1291	CH ₃ -		H	CH ₃ -
A1292	CH ₃ -		H	CH ₃ -
A1293	CH ₃ -		H	CH ₃ -
A1294	CH ₃ -		H	CH ₃ -
A1295	CH ₃ -		H	CH ₃ -
A1296	CH ₃ -		H	CH ₃ -
A1297	CH ₃ -		H	CH ₃ -
A1298	CH ₃ -		H	CH ₃ -
A1299	CH ₃ -		H	CH ₃ -
A1300	CH ₃ -		H	CH ₃ -
A1301	CH ₃ -		H	CH ₃ -
A1302	CH ₃ -		H	CH ₃ -

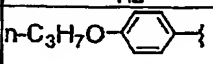
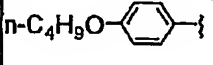
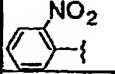
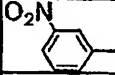
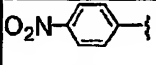
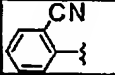
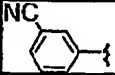
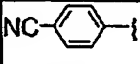
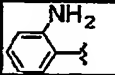
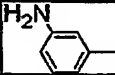
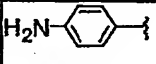
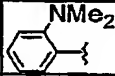
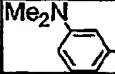
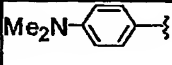
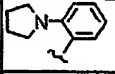
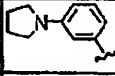
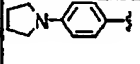
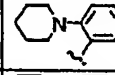
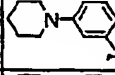
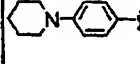
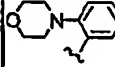
No.	R1	R2	R3	R4
A1303	CH ₃ -		H	CH ₃ -
A1304	CH ₃ -		H	CH ₃ -
A1305	CH ₃ -		H	CH ₃ -
A1306	CH ₃ -		H	CH ₃ -
A1307	CH ₃ -		H	CH ₃ -
A1308	CH ₃ -		H	CH ₃ -
A1309	CH ₃ -		H	CH ₃ -
A1310	CH ₃ -		H	CH ₃ -
A1311	CH ₃ -		H	CH ₃ -
A1312	CH ₃ -		H	CH ₃ -
A1313	CH ₃ -		H	CH ₃ -
A1314	CH ₃ -		H	CH ₃ -
A1315	CH ₃ -		H	CH ₃ -
A1316	CH ₃ -		H	CH ₃ -
A1317	CH ₃ -		H	CH ₃ -
A1318	CH ₃ -		H	CH ₃ -
A1319	CH ₃ -		H	CH ₃ -
A1320	CH ₃ -		H	CH ₃ -
A1321	CH ₃ -		H	CH ₃ -
A1322	CH ₃ -		H	CH ₃ -
A1323	CH ₃ -		H	CH ₃ -

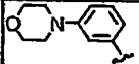
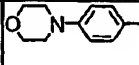
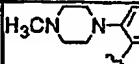
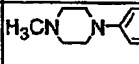
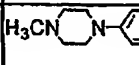
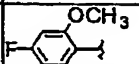
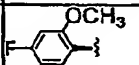
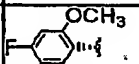
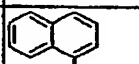
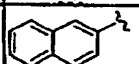

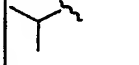
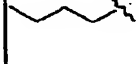
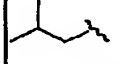
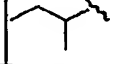

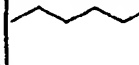
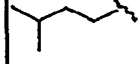
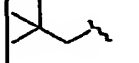
No.	R1	R2	R3	R4
A1324	CH3-		H	CH3-
A1325	CH3-		H	CH3-
A1326	CH3-		H	CH3-
A1327	CH3-		H	CH3-
A1328	CH3-		H	CH3-
A1329	CH3-		H	CH3-
A1330	CH3-		H	CH3-
A1331	CH3-		H	CH3-
A1332	CH3-		H	CH3-
A1333	CH3-		H	CH3-
A1334	CH3-		H	CH3-
A1335	CH3-		H	CH3-
A1336	CH3-		H	CH3-
A1337	CH3-		H	CH3-
A1338	CH3-		H	CH3-
A1339	CH3-		H	CH3-
A1340	CH3-		H	CH3-
A1341	CH3-		H	CH3-
A1342	CH3-		H	CH3-
A1343	CH3-		H	CH3-
A1344	CH3CH2-	CH3-	H	H





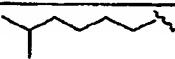


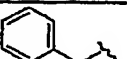
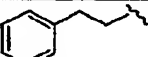
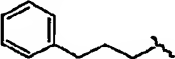



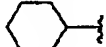
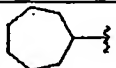






No.	R1	R2	R3	R4
A1345	CH ₃ CH ₂ -	CH ₃ CH ₂ -	H	H
A1346	CH ₃ CH ₂ -		H	H
A1347	CH ₃ CH ₂ -		H	H
A1348	CH ₃ CH ₂ -		H	H
A1349	CH ₃ CH ₂ -		H	H
A1350	CH ₃ CH ₂ -		H	H
A1351	CH ₃ CH ₂ -		H	H
A1352	CH ₃ CH ₂ -		H	H
A1353	CH ₃ CH ₂ -		H	H
A1354	CH ₃ CH ₂ -		H	H
A1355	CH ₃ CH ₂ -		H	H
A1356	CH ₃ CH ₂ -		H	H
A1357	CH ₃ CH ₂ -		H	H
A1358	CH ₃ CH ₂ -		H	H
A1359	CH ₃ CH ₂ -		H	H
A1360	CH ₃ CH ₂ -		H	H
A1361	CH ₃ CH ₂ -		H	H
A1362	CH ₃ CH ₂ -		H	H
A1363	CH ₃ CH ₂ -		H	H
A1364	CH ₃ CH ₂ -		H	H
A1365	CH ₃ CH ₂ -		H	H

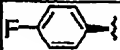

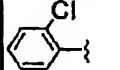
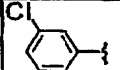
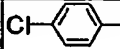
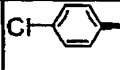
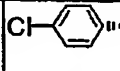
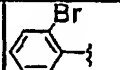
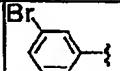
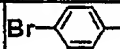
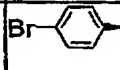
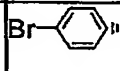
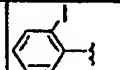
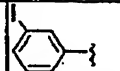

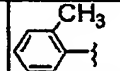
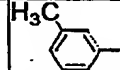
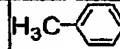
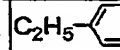
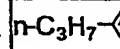
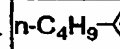
No.	R1	R2	R3	R4
A1366	CH ₃ CH ₂ -		H	H
A1367	CH ₃ CH ₂ -		H	H
A1368	CH ₃ CH ₂ -		H	H
A1369	CH ₃ CH ₂ -		H	H
A1370	CH ₃ CH ₂ -		H	H
A1371	CH ₃ CH ₂ -		H	H
A1372	CH ₃ CH ₂ -		H	H
A1373	CH ₃ CH ₂ -		H	H
A1374	CH ₃ CH ₂ -		H	H
A1375	CH ₃ CH ₂ -		H	H
A1376	CH ₃ CH ₂ -		H	H
A1377	CH ₃ CH ₂ -		H	H
A1378	CH ₃ CH ₂ -		H	H
A1379	CH ₃ CH ₂ -		H	H
A1380	CH ₃ CH ₂ -		H	H
A1381	CH ₃ CH ₂ -		H	H
A1382	CH ₃ CH ₂ -		H	H
A1383	CH ₃ CH ₂ -		H	H
A1384	CH ₃ CH ₂ -		H	H
A1385	CH ₃ CH ₂ -		H	H
A1386	CH ₃ CH ₂ -		H	H

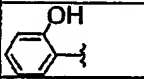
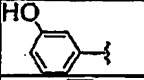
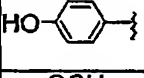
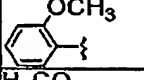
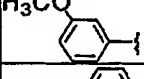
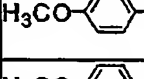
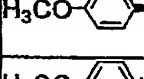
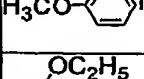
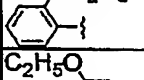
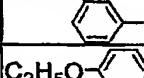
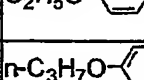
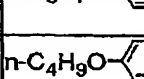
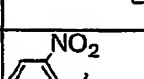
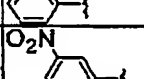
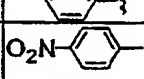
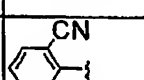
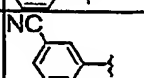
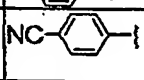
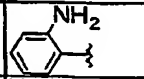
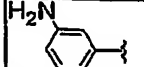

No.	R1	R2	R3	R4
A1387	CH ₃ CH ₂ -		H	H
A1388	CH ₃ CH ₂ -		H	H
A1389	CH ₃ CH ₂ -		H	H
A1390	CH ₃ CH ₂ -		H	H
A1391	CH ₃ CH ₂ -		H	H
A1392	CH ₃ CH ₂ -		H	H
A1393	CH ₃ CH ₂ -		H	H
A1394	CH ₃ CH ₂ -		H	H
A1395	CH ₃ CH ₂ -		H	H
A1396	CH ₃ CH ₂ -		H	H
A1397	CH ₃ CH ₂ -		H	H
A1398	CH ₃ CH ₂ -		H	H
A1399	CH ₃ CH ₂ -		H	H
A1400	CH ₃ CH ₂ -		H	H
A1401	CH ₃ CH ₂ -		H	H
A1402	CH ₃ CH ₂ -		H	H
A1403	CH ₃ CH ₂ -		H	H
A1404	CH ₃ CH ₂ -		H	H
A1405	CH ₃ CH ₂ -		H	H
A1406	CH ₃ CH ₂ -		H	H
A1407	CH ₃ CH ₂ -		H	H

No.	R1	R2	R3	R4
A1408	CH ₃ CH ₂ -		H	H
A1409	CH ₃ CH ₂ -		H	H
A1410	CH ₃ CH ₂ -		H	H
A1411	CH ₃ CH ₂ -		H	H
A1412	CH ₃ CH ₂ -		H	H
A1413	CH ₃ CH ₂ -		H	H
A1414	CH ₃ CH ₂ -		H	H
A1415	CH ₃ CH ₂ -		H	H
A1416	CH ₃ CH ₂ -		H	H
A1417	CH ₃ CH ₂ -		H	H
A1418	CH ₃ CH ₂ -		H	H
A1419	CH ₃ CH ₂ -		H	H
A1420	CH ₃ CH ₂ -		H	H
A1421	CH ₃ CH ₂ -		H	H
A1422	CH ₃ CH ₂ -		H	H
A1423	CH ₃ CH ₂ -		H	H
A1424	CH ₃ CH ₂ -		H	H
A1425	CH ₃ CH ₂ -		H	H
A1426	CH ₃ CH ₂ -		H	H
A1427	CH ₃ CH ₂ -		H	H
A1428	CH ₃ CH ₂ -		H	H

No.	R1	R2	R3	R4
A1429	CH ₃ CH ₂ -		H	H
A1430	CH ₃ CH ₂ -		H	H
A1431	CH ₃ CH ₂ -		H	H
A1432	CH ₃ CH ₂ -		H	H
A1433	CH ₃ CH ₂ -		H	H
A1434	CH ₃ CH ₂ -		H	H
A1435	CH ₃ CH ₂ -		H	H
A1436	CH ₃ CH ₂ -		H	H
A1437	CH ₃ CH ₂ -		H	H
A1438	CH ₃ CH ₂ -		H	H
A1439	CH ₃ CH ₂ -	CH ₃ -	H	CH ₃ -
A1440	CH ₃ CH ₂ -	CH ₃ CH ₂ -	H	CH ₃ -
A1441	CH ₃ CH ₂ -		H	CH ₃ -
A1442	CH ₃ CH ₂ -		H	CH ₃ -
A1443	CH ₃ CH ₂ -		H	CH ₃ -
A1444	CH ₃ CH ₂ -		H	CH ₃ -
A1445	CH ₃ CH ₂ -		H	CH ₃ -
A1446	CH ₃ CH ₂ -		H	CH ₃ -
A1447	CH ₃ CH ₂ -		H	CH ₃ -
A1448	CH ₃ CH ₂ -		H	CH ₃ -
A1449	CH ₃ CH ₂ -		H	CH ₃ -

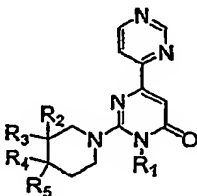



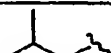






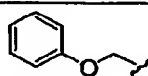
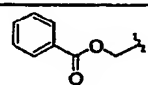
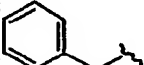
No.	R1	R2	R3	R4
A1450	CH ₃ CH ₂ -		H	CH ₃ -
A1451	CH ₃ OH ₂ -		H	CH ₃ -
A1452	CH ₃ CH ₂ -		H	CH ₃ -
A1453	CH ₃ CH ₂ -		H	CH ₃ -
A1454	CH ₃ CH ₂ -		H	CH ₃ -
A1455	CH ₃ OH ₂ -		H	CH ₃ -
A1456	CH ₃ CH ₂ -		H	CH ₃ -
A1457	CH ₃ CH ₂ -		H	CH ₃ -
A1458	CH ₃ CH ₂ -		H	CH ₃ -
A1459	CH ₃ CH ₂ -		H	CH ₃ -
A1460	CH ₃ CH ₂ -		H	CH ₃ -
A1461	CH ₃ CH ₂ -		H	CH ₃ -
A1462	CH ₃ CH ₂ -		H	CH ₃ -
A1463	CH ₃ CH ₂ -		H	CH ₃ -
A1464	CH ₃ CH ₂ -		H	CH ₃ -
A1465	CH ₃ CH ₂ -		H	CH ₃ -
A1466	CH ₃ CH ₂ -		H	CH ₃ -
A1467	CH ₃ CH ₂ -		H	CH ₃ -
A1468	CH ₃ CH ₂ -		H	CH ₃ -
A1469	CH ₃ CH ₂ -		H	CH ₃ -
A1470	CH ₃ CH ₂ -		H	CH ₃ -

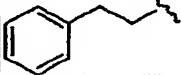
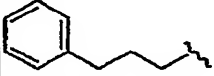
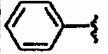
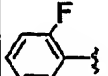
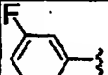

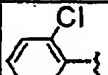
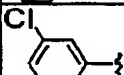
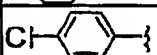
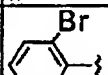
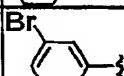

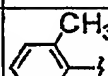
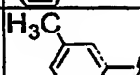
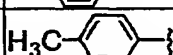
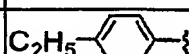
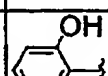
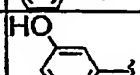
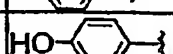
No.	R1	R2	R3	R4
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A1472	CH ₃ CH ₂ -		H	CH ₃ -
A1473	CH ₃ CH ₂ -		H	CH ₃ -
A1474	CH ₃ CH ₂ -		H	CH ₃ -
A1475	CH ₃ CH ₂ -		H	CH ₃ -
A1476	CH ₃ CH ₂ -		H	CH ₃ -
A1477	CH ₃ CH ₂ -		H	CH ₃ -
A1478	CH ₃ CH ₂ -		H	CH ₃ -
A1479	CH ₃ CH ₂ -		H	CH ₃ -
A1480	CH ₃ CH ₂ -		H	CH ₃ -
A1481	CH ₃ CH ₂ -		H	CH ₃ -
A1482	CH ₃ CH ₂ -		H	CH ₃ -
A1483	CH ₃ CH ₂ -		H	CH ₃ -
A1484	CH ₃ CH ₂ -		H	CH ₃ -
A1485	CH ₃ CH ₂ -		H	CH ₃ -
A1486	CH ₃ CH ₂ -		H	CH ₃ -
A1487	CH ₃ CH ₂ -		H	CH ₃ -
A1488	CH ₃ CH ₂ -		H	CH ₃ -
A1489	CH ₃ CH ₂ -		H	CH ₃ -
A1490	CH ₃ CH ₂ -		H	CH ₃ -
A1491	CH ₃ CH ₂ -		H	CH ₃ -

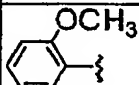
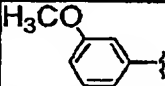
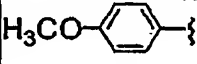
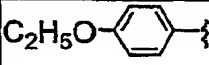
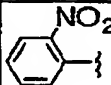
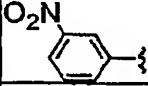
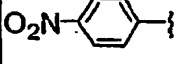
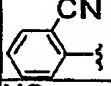
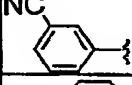
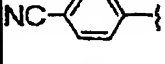
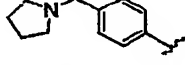
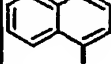
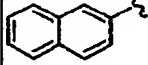
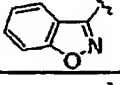
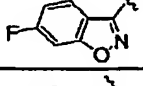
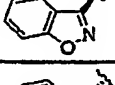
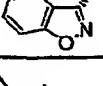

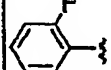
No.	R1	R2	R3	R4
A1492	CH ₃ CH ₂ -		H	CH ₃ -
A1493	CH ₃ CH ₂ -		H	CH ₃ -
A1494	CH ₃ CH ₂ -		H	CH ₃ -
A1495	CH ₃ CH ₂ -		H	CH ₃ -
A1496	CH ₃ CH ₂ -		H	CH ₃ -
A1497	CH ₃ CH ₂ -		H	CH ₃ -
A1498	CH ₃ CH ₂ -		H	CH ₃ -
A1499	CH ₃ CH ₂ -		H	CH ₃ -
A1500	CH ₃ CH ₂ -		H	CH ₃ -
A1501	CH ₃ CH ₂ -		H	CH ₃ -
A1502	CH ₃ CH ₂ -		H	CH ₃ -
A1503	CH ₃ CH ₂ -		H	CH ₃ -
A1504	CH ₃ CH ₂ -		H	CH ₃ -
A1505	CH ₃ CH ₂ -		H	CH ₃ -
A1506	CH ₃ CH ₂ -		H	CH ₃ -
A1507	CH ₃ CH ₂ -		H	CH ₃ -
A1508	CH ₃ CH ₂ -		H	CH ₃ -
A1509	CH ₃ CH ₂ -		H	CH ₃ -
A1510	CH ₃ CH ₂ -		H	CH ₃ -
A1511	CH ₃ CH ₂ -		H	CH ₃ -
A1512	CH ₃ CH ₂ -		H	CH ₃ -

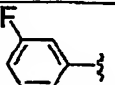
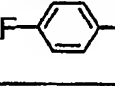
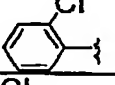
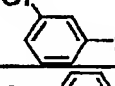
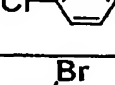
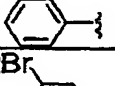
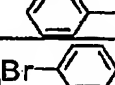
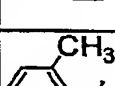
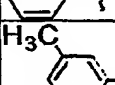
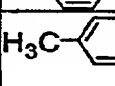
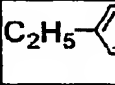
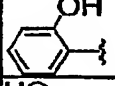
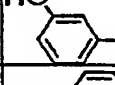
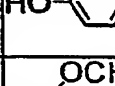
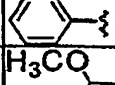
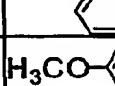
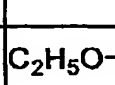


No.	R1	R2	R3	R4
A1513	CH ₃ CH ₂ -		H	CH ₃ -
A1514	CH ₃ CH ₂ -		H	CH ₃ -
A1515	CH ₃ CH ₂ -		H	CH ₃ -
A1516	CH ₃ CH ₂ -		H	CH ₃ -
A1517	CH ₃ CH ₂ -		H	CH ₃ -
A1518	CH ₃ CH ₂ -		H	CH ₃ -
A1519	CH ₃ CH ₂ -		H	CH ₃ -
A1520	CH ₃ CH ₂ -		H	CH ₃ -
A1521	CH ₃ CH ₂ -		H	CH ₃ -
A1522	CH ₃ CH ₂ -		H	CH ₃ -
A1523	CH ₃ CH ₂ -		H	CH ₃ -
A1524	CH ₃ CH ₂ -		H	CH ₃ -
A1525	CH ₃ CH ₂ -		H	CH ₃ -
A1526	CH ₃ CH ₂ -		H	CH ₃ -
A1527	CH ₃ CH ₂ -		H	CH ₃ -
A1528	CH ₃ CH ₂ -		H	CH ₃ -
A1529	CH ₃ CH ₂ -		H	CH ₃ -
A1530	CH ₃ CH ₂ -		H	CH ₃ -
A1531	CH ₃ CH ₂ -		H	CH ₃ -
A1532	CH ₃ CH ₂ -		H	CH ₃ -
A1533	CH ₃ CH ₂ -		H	CH ₃ -

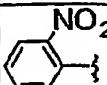
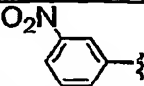
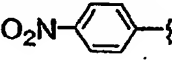
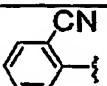
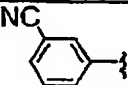
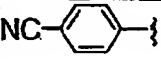
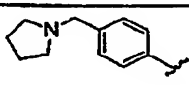
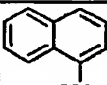
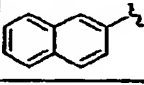
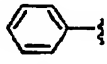
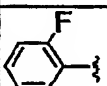
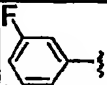
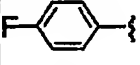
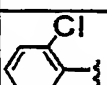
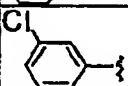
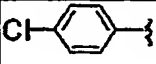
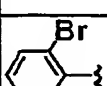
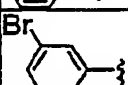
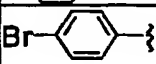
Table-2

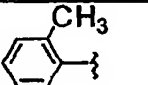
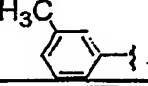
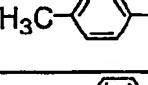
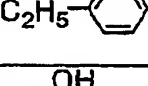
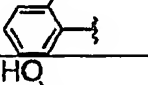
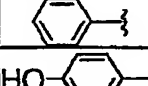
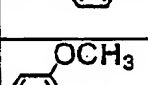
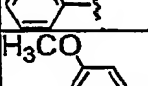
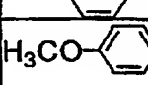
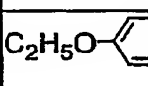
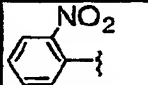
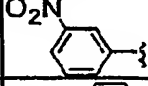
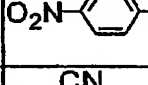
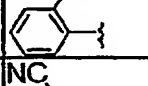
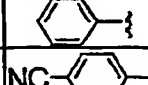
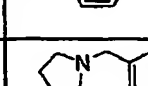
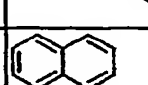
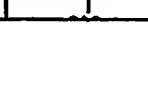

					
No.	R1	R2	R3	R4	R5
B1	CH3-	CH3-	H	H	H
B2	CH3-	CH3CH2-	H	H	H
B3	CH3-		H	H	H
B4	CH3-		H	H	H
B5	CH3-		H	H	H
B6	CH3-		H	H	H
B7	CH3-		H	H	H
B8	CH3-		H	H	H
B9	CH3-		H	H	H
B10	CH3-		H	H	H
B11	CH3-		H	H	H
B12	CH3-		H	H	H
B13	CH3-		H	H	H
B14	CH3-		H	H	H
B15	CH3-		H	H	H

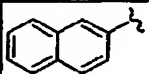






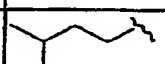



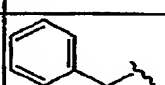
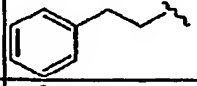
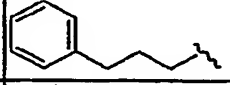
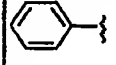
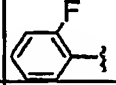
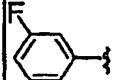
No.	R1	R2	R3	R4	R5
B16	CH3-		H	H	H
B17	CH3-		H	H	H
B18	CH3-		H	H	H
B19	CH3-		H	H	H
B20	CH3-		H	H	H
B21	CH3-		H	H	H
B22	CH3-		H	H	H
B23	CH3-		H	H	H
B24	CH3-		H	H	H
B25	CH3-		H	H	H
B26	CH3-		H	H	H
B27	CH3-		H	H	H
B28	CH3-		H	H	H
B29	CH3-		H	H	H
B30	CH3-		H	H	H
B31	CH3-		H	H	H
B32	CH3-		H	H	H
B33	CH3-		H	H	H
B34	CH3-		H	H	H



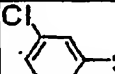
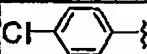
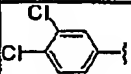

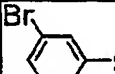
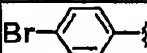

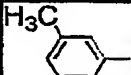
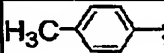
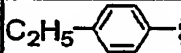

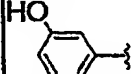
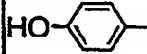
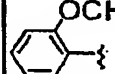
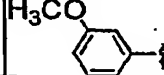
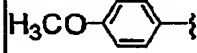
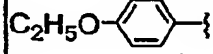
No.	R1	R2	R3	R4	R5
B35	CH3-		H	H	H
B36	CH3-		H	H	H
B37	CH3-		H	H	H
B38	CH3-		H	H	H
B39	CH3-		H	H	H
B40	CH3-		H	H	H
B41	CH3-		H	H	H
B42	CH3-		H	H	H
B43	CH3-		H	H	H
B44	CH3-		H	H	H
B45	CH3-		H	H	H
B46	CH3-		H	H	H
B47	CH3-		H	H	H
B48	CH3-		H	H	H
B49	CH3-		H	H	H
B50	CH3-		H	H	H
B51	CH3-		H	H	H
B52	CH3-		OH	H	H
B53	CH3-		OH	H	H

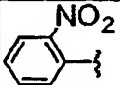
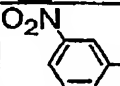
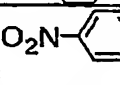
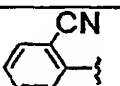
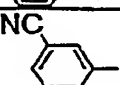
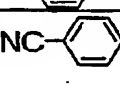
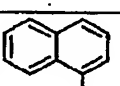
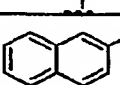
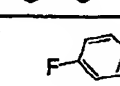
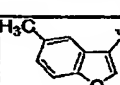
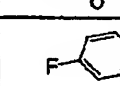
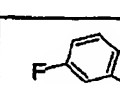
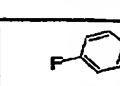
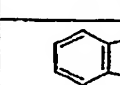
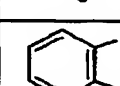
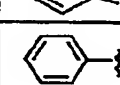
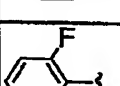
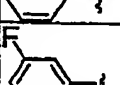
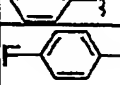
No.	R1	R2	R3	R4	R5
B54	CH ₃ -		OH	H	H
B55	CH ₃ -		OH	H	H
B56	CH ₃ -		OH	H	H
B57	CH ₃ -		OH	H	H
B58	CH ₃ -		OH	H	H
B59	CH ₃ -		OH	H	H
B60	CH ₃ -		OH	H	H
B61	CH ₃ -		OH	H	H
B62	CH ₃ -		OH	H	H
B63	CH ₃ -		OH	H	H
B64	CH ₃ -		OH	H	H
B65	CH ₃ -		OH	H	H
B66	CH ₃ -		OH	H	H
B67	CH ₃ -		OH	H	H
B68	CH ₃ -		OH	H	H
B69	CH ₃ -		OH	H	H
B70	CH ₃ -		OH	H	H
B71	CH ₃ -		OH	H	H
B72	CH ₃ -		OH	H	H

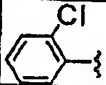
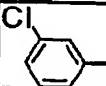
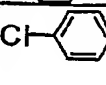
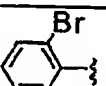
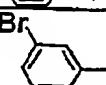
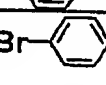
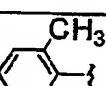
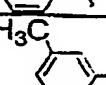
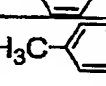
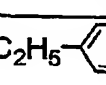
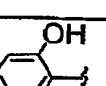
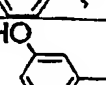
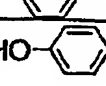
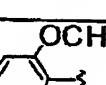
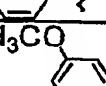
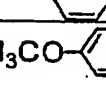
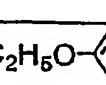
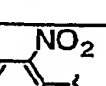
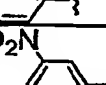
No.	R1	R2	R3	R4	R5
B73	CH3-		OH	H	H
B74	CH3-		OH	H	H
B75	CH3-		OH	H	H
B76	CH3-		OH	H	H
B77	CH3-		OH	H	H
B78	CH3-		OH	H	H
B79	CH3-		OH	H	H
B80	CH3-		OH	H	H
B81	CH3-		OH	H	H
B82	CH3-		CN	H	H
B83	CH3-		CN	H	H
B84	CH3-		CN	H	H
B85	CH3-		CN	H	H
B86	CH3-		CN	H	H
B87	CH3-		CN	H	H
B88	CH3-		CN	H	H
B89	CH3-		CN	H	H
B90	CH3-		CN	H	H
B91	CH3-		CN	H	H

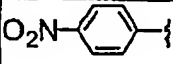
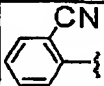
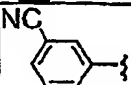
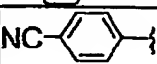
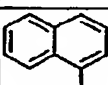
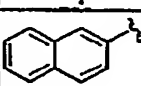
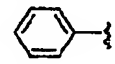
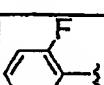
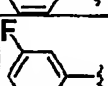
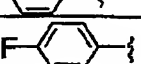
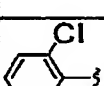
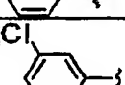
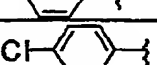
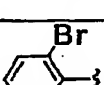
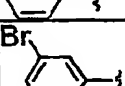
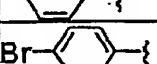
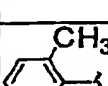
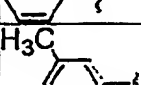
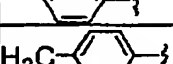
No.	R1	R2	R3	R4	R5
B92	CH ₃ -		CN	H	H
B93	CH ₃ -		CN	H	H
B94	CH ₃ -		CN	H	H
B95	CH ₃ -		CN	H	H
B96	CH ₃ -		CN	H	H
B97	CH ₃ -		CN	H	H
B98	CH ₃ -		CN	H	H
B99	CH ₃ -		CN	H	H
B100	CH ₃ -		CN	H	H
B101	CH ₃ -		CN	H	H
B102	CH ₃ -		CN	H	H
B103	CH ₃ -		CN	H	H
B104	CH ₃ -		CN	H	H
B105	CH ₃ -		CN	H	H
B106	CH ₃ -		CN	H	H
B107	CH ₃ -		CN	H	H
B108	CH ₃ -		CN	H	H
B109	CH ₃ -		CN	H	H
B110	CH ₃ -		CN	H	H

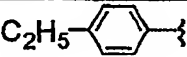
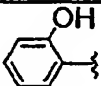
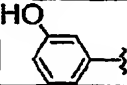
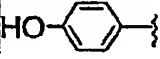
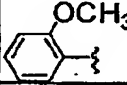
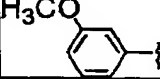
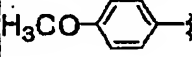
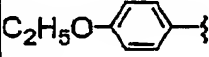
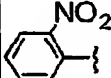
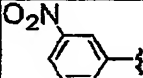
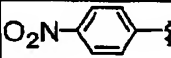
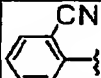
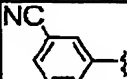
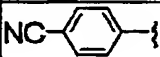
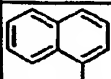
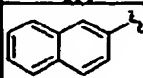


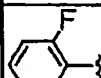

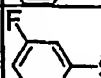

No.	R1	R2	R3	R4	R5
B111	CH3-		CN	H	H
B112	CH3-	H	H	CH3-	H
B113	CH3-	H	H	CH3CH2-	H
B114	CH3-	H	H		H
B115	CH3-	H	H		H
B116	CH3-	H	H		H
B117	CH3-	H	H		H
B118	CH3-	H	H		H
B119	CH3-	H	H		H
B120	CH3-	H	H		H
B121	CH3-	H	H		H
B122	CH3-	H	H		H
B123	CH3-	H	H		H
B124	CH3-	H	H		H
B125	CH3-	H	H		H
B126	CH3-	H	H		H
B127	CH3-	H	H		H
B128	CH3-	H	H		H
B129	CH3-	H	H		H



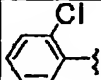

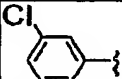

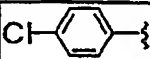

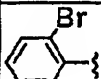

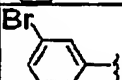

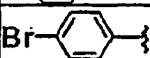

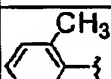

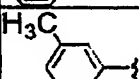

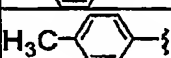

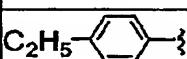

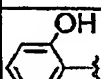

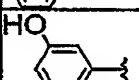

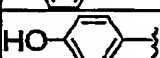

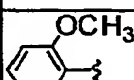

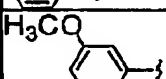

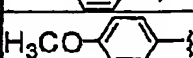

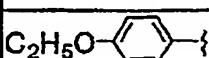

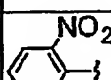

No.	R1	R2	R3	R4	R5
B130	CH ₃ -	H	H		H
B131	CH ₃ -	H	H		H
B132	CH ₃ -	H	H		H
B133	CH ₃ -	H	H		H
B134	CH ₃ -	H	H		H
B135	CH ₃ -	H	H		H
B136	CH ₃ -	H	H		H
B137	CH ₃ -	H	H		H
B138	CH ₃ -	H	H		H
B139	CH ₃ -	H	H		H
B140	CH ₃ -	H	H		H
B141	CH ₃ -	H	H		H
B142	CH ₃ -	H	H		H
B143	CH ₃ -	H	H		H
B144	CH ₃ -	H	H		H
B145	CH ₃ -	H	H		H
B146	CH ₃ -	H	H		H
B147	CH ₃ -	H	H		H
B148	CH ₃ -	H	H		H

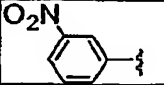

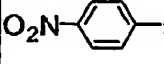



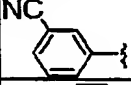

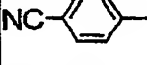



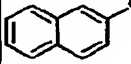

No.	R1	R2	R3	R4	R5
B149	CH3-	H	H		H
B150	CH3-	H	H		H
B151	CH3-	H	H		H
B152	CH3-	H	H		H
B153	CH3-	H	H		H
B154	CH3-	H	H		H
B155	CH3-	H	H		H
B156	CH3-	H	H		H
B157	CH3-	H	H		H
B158	CH3-	H	H		H
B159	CH3-	H	H		H
B160	CH3-	H	H		H
B161	CH3-	H	H		H
B162	CH3-	H	H		H
B163	CH3-	H	H		H
B164	CH3-	H	H		OH
B165	CH3-	H	H		OH
B166	CH3-	H	H		OH
B167	CH3-	H	H		OH

No.	R1	R2	R3	R4	R5
B168	CH ₃ -	H	H		OH
B169	CH ₃ -	H	H		OH
B170	CH ₃ -	H	H		OH
B171	CH ₃ -	H	H		OH
B172	CH ₃ -	H	H		OH
B173	CH ₃ -	H	H		OH
B174	CH ₃ -	H	H		OH
B175	CH ₃ -	H	H		OH
B176	CH ₃ -	H	H		OH
B177	CH ₃ -	H	H		OH
B178	CH ₃ -	H	H		OH
B179	CH ₃ -	H	H		OH
B180	CH ₃ -	H	H		OH
B181	CH ₃ -	H	H		OH
B182	CH ₃ -	H	H		OH
B183	CH ₃ -	H	H		OH
B184	CH ₃ -	H	H		OH
B185	CH ₃ -	H	H		OH
B186	CH ₃ -	H	H		OH

No.	R1	R2	R3	R4	R5
B187	CH ₃ -	H	H		OH
B188	CH ₃ -	H	H		OH
B189	CH ₃ -	H	H		OH
B190	CH ₃ -	H	H		OH
B191	CH ₃ -	H	H		OH
B192	CH ₃ -	H	H		OH
B193	CH ₃ -	H	H		CN
B194	CH ₃ -	H	H		CN
B195	CH ₃ -	H	H		CN
B196	CH ₃ -	H	H		CN
B197	CH ₃ -	H	H		CN
B198	CH ₃ -	H	H		CN
B199	CH ₃ -	H	H		CN
B200	CH ₃ -	H	H		CN
B201	CH ₃ -	H	H		CN
B202	CH ₃ -	H	H		CN
B203	CH ₃ -	H	H		CN
B204	CH ₃ -	H	H		CN
B205	CH ₃ -	H	H		CN

No.	R1	R2	R3	R4	R5
B206	CH ₃ -	H	H		CN
B207	CH ₃ -	H	H		CN
B208	CH ₃ -	H	H		CN
B209	CH ₃ -	H	H		CN
B210	CH ₃ -	H	H		CN
B211	CH ₃ -	H	H		CN
B212	CH ₃ -	H	H		CN
B213	CH ₃ -	H	H		CN
B214	CH ₃ -	H	H		CN
B215	CH ₃ -	H	H		CN
B216	CH ₃ -	H	H		CN
B217	CH ₃ -	H	H		CN
B218	CH ₃ -	H	H		CN
B219	CH ₃ -	H	H		CN
B220	CH ₃ -	H	H		CN
B221	CH ₃ -	H	H		CN
B222	CH ₃ -	H	H		
B223	CH ₃ -	H	H		
B224	CH ₃ -	H	H		

No.	R1	R2	R3	R4	R5
B225	CH ₃ -	H	H		
B226	CH ₃ -	H	H		
B227	CH ₃ -	H	H		
B228	CH ₃ -	H	H		
B229	CH ₃ -	H	H		
B230	CH ₃ -	H	H		
B231	CH ₃ -	H	H		
B232	CH ₃ -	H	H		
B233	CH ₃ -	H	H		
B234	CH ₃ -	H	H		
B235	CH ₃ -	H	H		
B236	CH ₃ -	H	H		
B237	CH ₃ -	H	H		
B238	CH ₃ -	H	H		
B239	CH ₃ -	H	H		
B240	CH ₃ -	H	H		
B241	CH ₃ -	H	H		
B242	CH ₃ -	H	H		
B243	CH ₃ -	H	H		

No.	R1	R2	R3	R4	R5
B244	CH ₃ -	H	H		
B245	CH ₃ -	H	H		
B246	CH ₃ -	H	H		
B247	CH ₃ -	H	H		
B248	CH ₃ -	H	H		
B249	CH ₃ -	H	H		
B250	CH ₃ -	H	H		

Particularly preferred compounds of the present invention represented by formula (I) include:

2-(3-Phenylpiperazin-1-yl)-3-methyl-6-(4-pyrimidyl)-3*H*-pyrimidin-4-one;
2-(3-(4-Fluorophenyl)piperazin-1-yl)-3-methyl-6-(4-pyrimidyl)-3*H*-pyrimidin-4-one;
2-(3-(3-Fluorophenyl)piperazin-1-yl)-3-methyl-6-(4-pyrimidyl)-3*H*-pyrimidin-4-one;
2-(3-(2-Fluorophenyl)piperazin-1-yl)-3-methyl-6-(4-pyrimidyl)-3*H*-pyrimidin-4-one;
2-(3-(4-Chlorophenyl)piperazin-1-yl)-3-methyl-6-(4-pyrimidyl)-3*H*-pyrimidin-4-one;
2-(3-(3-Chlorophenyl)piperazin-1-yl)-3-methyl-6-(4-pyrimidyl)-3*H*-pyrimidin-4-one;
2-(3-(2-Chlorophenyl)piperazin-1-yl)-3-methyl-6-(4-pyrimidyl)-3*H*-pyrimidin-4-one;
2-(3-(4-Bromophenyl)piperazin-1-yl)-3-methyl-6-(4-pyrimidyl)-3*H*-pyrimidin-4-one;
2-(3-(3-Bromophenyl)piperazin-1-yl)-3-methyl-6-(4-pyrimidyl)-3*H*-pyrimidin-4-one;
2-(3-(2-Bromophenyl)piperazin-1-yl)-3-methyl-6-(4-pyrimidyl)-3*H*-pyrimidin-4-one;
2-(3-(4-Cyanophenyl)piperazin-1-yl)-3-methyl-6-(4-pyrimidyl)-3*H*-pyrimidin-4-one;
2-(3-(3-Cyanophenyl)piperazin-1-yl)-3-methyl-6-(4-pyrimidyl)-3*H*-pyrimidin-4-one;
2-(3-(2-Cyanophenyl)piperazin-1-yl)-3-methyl-6-(4-pyrimidyl)-3*H*-pyrimidin-4-one;
2-(3-(4-Methoxyphenyl)piperazin-1-yl)-3-methyl-6-(4-pyrimidyl)-3*H*-pyrimidin-4-one;
2-(3-(3-Methoxyphenyl)piperazin-1-yl)-3-methyl-6-(4-pyrimidyl)-3*H*-pyrimidin-4-one;
2-(3-(2-Methoxyphenyl)piperazin-1-yl)-3-methyl-6-(4-pyrimidyl)-3*H*-pyrimidin-4-one;
2-(3-(2-Ethoxyphenyl)piperazin-1-yl)-3-methyl-6-(4-pyrimidyl)-3*H*-pyrimidin-4-one;
2-(3-(6-Fluoro-2-methoxyphenyl)piperazin-1-yl)-3-methyl-6-(4-pyrimidyl)-3*H*-pyrimidin-4-one;

2-(3-(5-Fluoro-2-methoxyphenyl)piperazin-1-yl)-3-methyl-6-(4-pyrimidyl)-3H-pyrimidin-4-one;
2-(3-(4-Fluoro-2-methoxyphenyl)piperazin-1-yl)-3-methyl-6-(4-pyrimidyl)-3H-pyrimidin-4-one;
(S)-2-(3-(4-Fluoro-2-methoxyphenyl)piperazin-1-yl)-3-methyl-6-(4-pyrimidyl)-3H-pyrimidin-4-one;
(R)-2-(3-(4-Fluoro-2-methoxyphenyl)piperazin-1-yl)-3-methyl-6-(4-pyrimidyl)-3H-pyrimidin-4-one;
2-(3-(4-Chloro-2-methoxyphenyl)piperazin-1-yl)-3-methyl-6-(4-pyrimidyl)-3H-pyrimidin-4-one;
2-(3-(5-Bromo-2-methoxyphenyl)piperazin-1-yl)-3-methyl-6-(4-pyrimidyl)-3H-pyrimidin-4-one;
2-(3-(2,6-Dichlorophenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3H-pyrimidin-4-one;
2-(3-(2,4-Dimethoxyphenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3H-pyrimidin-4-one;
2-(3-(3,4-Dimethoxyphenyl)piperazin-1-yl)-3-methyl-6-(4-pyrimidyl)-3H-pyrimidin-4-one;
2-(3-(2,5-Dimethoxyphenyl)piperazin-1-yl)-3-methyl-6-(4-pyrimidyl)-3H-pyrimidin-4-one;
2-(3-(2,6-Dimethoxyphenyl)piperazin-1-yl)-3-methyl-6-(4-pyrimidyl)-3H-pyrimidin-4-one;
2-(3-(2,4-Difluoro-6-methoxyphenyl)piperazin-1-yl)-3-methyl-6-(4-pyrimidyl)-3H-pyrimidin-4-one;
2-(3-(1-Naphthyl)piperazin-1-yl)-3-methyl-6-(4-pyrimidyl)-3H-pyrimidin-4-one;
2-(3-(2-Naphthyl)piperazin-1-yl)-3-methyl-6-(4-pyrimidyl)-3H-pyrimidin-4-one;
2-(3-(2,3-Dihydrobenzofuran-7-yl)piperazin-1-yl)-3-methyl-6-(4-pyrimidyl)-3H-pyrimidin-4-one;
2-(3-(Benzofuran-2-yl)piperazin-1-yl)-3-methyl-6-(4-pyrimidyl)-3H-pyrimidin-4-one;
2-(3-(4-(Pyrrolidin-1-yl-methyl)phenyl)piperazin-1-yl)-3-methyl-6-(4-pyrimidyl)-3H-pyrimidin-4-one;
2-(3-(4-(Pyrrolidin-1-yl)phenyl)piperazin-1-yl)-3-methyl-6-(4-pyrimidyl)-3H-pyrimidin-4-one;

2-(3-(2-methoxy-4-(pyrrolidin-1-yl)phenyl)piperazin-1-yl)-3-methyl-6-(4-pyrimidyl)-3*H*-pyrimidin-4-one;
2-(3-(2-methoxy-5-(pyrrolidin-1-yl)phenyl)piperazin-1-yl)-3-methyl-6-(4-pyrimidyl)-3*H*-pyrimidin-4-one;
2-(3-(4-(Phenyl)phenyl)piperazin-1-yl)-3-methyl-6-(4-pyrimidyl)-3*H*-pyrimidin-4-one;
2-(3-(4-(4-Fluorophenyl)phenyl)piperazin-1-yl)-3-methyl-6-(4-pyrimidyl)-3*H*-pyrimidin-4-one;
2-(3-(4-(4-Methoxyphenyl)phenyl)piperazin-1-yl)-3-methyl-6-(4-pyrimidyl)-3*H*-pyrimidin-4-one;
2-(3-(4-(2-Methoxyphenyl)phenyl)piperazin-1-yl)-3-methyl-6-(4-pyrimidyl)-3*H*-pyrimidin-4-one;
2-(3-(4-(Morpholin-4-yl)phenyl)piperazin-1-yl)-3-methyl-6-(4-pyrimidyl)-3*H*-pyrimidin-4-one;
2-(3-(4-(4-Methylpiperazin-1-yl)phenyl)piperazin-1-yl)-3-methyl-6-(4-pyrimidyl)-3*H*-pyrimidin-4-one;
2-(3-(4-Fluoro-2-methoxyphenyl)-4-methylpiperazin-1-yl)-3-methyl-6-(4-pyrimidyl)-3*H*-pyrimidin-4-one;
(*S*)-2-(3-(4-Fluoro-2-methoxyphenyl)-4-methylpiperazin-1-yl)-3-methyl-6-(4-pyrimidyl)-3*H*-pyrimidin-4-one;
(*R*)-2-(3-(4-Fluoro-2-methoxyphenyl)-4-methylpiperazin-1-yl)-3-methyl-6-(4-pyrimidyl)-3*H*-pyrimidin-4-one;
2-(4-Acetyl-3-(4-fluoro-2-methoxyphenyl)piperazin-1-yl)-3-methyl-6-(4-pyrimidyl)-3*H*-pyrimidin-4-one;
2-(4-Benzyl-3-(4-fluoro-2-methoxyphenyl)piperazin-1-yl)-3-methyl-6-(4-pyrimidyl)-3*H*-pyrimidin-4-one;
2-(4-(4-Fluorophenyl)piperidin-1-yl)-3-methyl-6-(4-pyrimidyl)-3*H*-pyrimidin-4-one;
2-(4-Cyano-4-phenylpiperidin-1-yl)-3-methyl-6-(4-pyrimidyl)-3*H*-pyrimidin-4-one;
2-(4-(6-Fluorobenofuran-3-yl)piperidin-1-yl)-3-methyl-6-(4-pyrimidyl)-3*H*-pyrimidin-4-one;
2-(3-(Benzoisoxazol-3-yl)piperidin-1-yl)-3-methyl-6-(4-pyrimidyl)-3*H*-pyrimidin-4-one;
(*S*)-2-(3-(Benzoisoxazol-3-yl)piperidin-1-yl)-3-methyl-6-(4-pyrimidyl)-3*H*-pyrimidin-4-one;

(R)-2-(3-(Benzoisoxazol-3-yl)piperidin-1-yl)-3-methyl-6-(4-pyrimidyl)-3H-pyrimidin-4-one;

2-(3-(6-Fluorobenzoisoxazol-3-yl)piperidin-1-yl)-3-methyl-6-(4-pyrimidyl)-3H-pyrimidin-4-one;

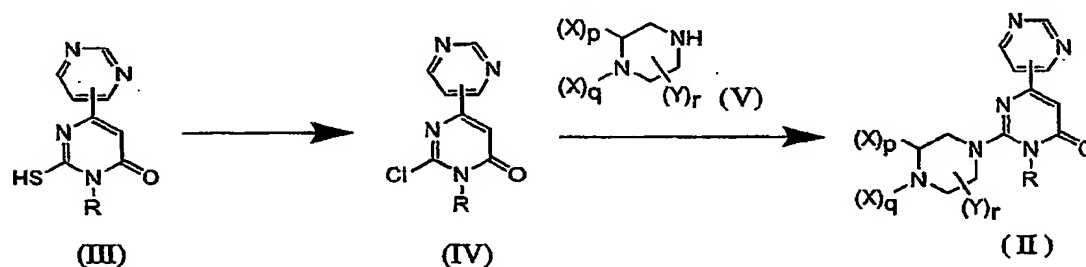
2-(4-(6-Fluorobenzoisoxazol-3-yl)piperidin-1-yl)-3-methyl-6-(4-pyrimidyl)-3H-pyrimidin-4-one;

2-(4-(5-Methylbenofuran-3-yl)piperidin-1-yl)-3-methyl-6-(4-pyrimidyl)-3H-pyrimidin-4-one; and

2-(4-(6-Fluorobenzothiophene-3-yl)piperidin-1-yl)-3-methyl-6-(4-pyrimidyl)-3H-pyrimidin-4-one.

Salts of the aforementioned preferred compound, and solvates or hydrates of the aforementioned compounds and salts thereof are also preferred.

The 3-substituted-4-pyrimidone compounds represented by the aforementioned formula (I) can be prepared, for example, according to the method explained below.



(In the above scheme, definitions of R, X and Y are the same as those already described.)

The 2-thiopyrimidinone represented by the above formula (III) is prepared easily by a modification of the method described in EP 354,179. The reaction may be carried out in the presence of a base such as sodium hydroxide, potassium hydroxide, sodium methoxide, sodium ethoxide, potassium tert-butoxide, sodium carbonate, sodium hydrogencarbonate, potassium carbonate, triethylamine, diisopropylethylamine, and 1,8-diazabicyclo[5,4,0]undec-7-en for 1 to 100 hours at a suitable temperature ranging from 0 °C to 200 °C under nitrogen or argon atmosphere or under ordinary air to afford the desired compound (III). Examples of a solvent for the reactions include, for example, alcoholic solvent such as

methanol, ethanol, 1-propanol, isopropanol, tert-butanol, ethylene glycol, propylene glycol; etheric solvents such as diethyl ether, tert-butyl methyl ether, tetrahydrofuran, isopropyl ether; hydrocarbonic solvents such as benzene, toluene, xylene; halogenated hydrocarbonic solvents such as dichloromethane, chloroform, dichloroethane; aprotic polar solvents such as formamide, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone, dimethyl sulfoxide, sulfolane, hexamethylphosphoric triamide, water and the like. Generally, a single solvent or a mixture of two or more solvents may be used so as to be suitable to a base used.

Then the 2-thiopyrimidone derivative (III) is transformed into the 2-chloropyrimidone (IV) by a chlorinating agent. The reaction time and temperature depend on the chlorinating agent used. Examples of a chlorinating agent for the reactions include, for example, thionyl chloride, thionyl chloride and dimethylformamide, phosphorus oxychloride, phosphorus oxychloride and dimethylformamide, oxalyl chloride, phosphorous oxychloride and dimethylformamide, and phosphorus pentachloride.

The amine represented by the above formula (V) may be prepared by a modification of the method described in Japanese Patent Unexamined Publication [Kokai] No. 52-139085/1977 or according to well-known methods of one skilled in the art.

Then the chloride derivative (IV) is allowed to react with the amine (V) or salts thereof in the presence of a base such as sodium hydroxide, potassium hydroxide, sodium methoxide, sodium ethoxide, sodium carbonate, sodium hydrogencarbonate, potassium carbonate, triethylamine, diisopropylethylamine, and 1,8-diazabicyclo[5,4,0]undec-7-en for 0.1 to 100 hours at a suitable temperature ranging from 0 °C to 200 °C under nitrogen or argon atmosphere or under ordinary air to afford the desired compound (II).

Examples of a solvent for the reactions include, for example, alcoholic solvent such as methanol, ethanol, 1-propanol, isopropanol, tert-butanol, ethylene glycol, propylene glycol; etheric solvents such as diethyl ether, tert-butyl methyl ether, tetrahydrofuran, isopropyl ether; hydrocarbonic solvents such as benzene, toluene, xylene; halogenated hydrocarbonic solvents such as dichloromethane, chloroform, dichloroethane; aprotic polar solvents such as formamide,

N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone, dimethyl sulfoxide, sulfolane, hexamethylphosphoric triamide, water and the like. Generally, a single solvent or a mixture of two or more solvents may be used so as to be suitable to a base used.

The compounds of the present invention have inhibitory activity against TPK1, and they inhibit TPK1 activity in neurodegenerative diseases like Alzheimer disease, thereby suppress the neurotoxicity of A β and the formation of PHF and inhibit the nerve cell death. Accordingly, the compounds of the present invention are useful as an active ingredient of a medicament which radically enables preventive and/or therapeutic treatment of Alzheimer disease. In addition, the compounds of the present invention are also useful as an active ingredient of a medicament for preventive and/or therapeutic treatment of ischemic cerebrovascular accidents, Down syndrome, cerebral bleeding due to solitary cerebral amyloid angiopathy, progressive supranuclear palsy, subacute sclerosing panencephalitis, postencephalitic parkinsonism, pugilistic encephalosis, Guam parkinsonism-dementia complex, Lewy body disease, Pick's disease, corticobasal degeneration frontotemporal dementia, vascular dementia, acute stroke and traumatic injuries, brain and spinal cord trauma, peripheral neuropathies, retinopathies and glaucoma, non-insulin dependent diabetes (such as diabetes type II), and obesity, manic depressive illness, schizophrenia, alopecia, cancers such as breast cancer, non-small cell lung carcinoma, thyroid cancer, T or B-cell leukemia and several virus-induced tumors.

As the active ingredient of the medicament of the present invention, a substance may be used which is selected from the group consisting of the compound represented by the aforementioned formula (I) and pharmacologically acceptable salts thereof, and solvates thereof and hydrates thereof. The substance, per se, may be administered as the medicament of the present invention, however, it is desirable to administer the medicament in a form of a pharmaceutical composition which comprises the aforementioned substance as an active ingredient and one or more of pharmaceutical additives. As the active ingredient of the medicament of the present invention, two or more of the aforementioned substance may be used in combination. The above pharmaceutical composition may be supplemented with an

active ingredient of other medicament for the treatment of, for example, Alzheimer disease, vascular dementia, acute stroke and traumatic injuries, brain and spinal cord trauma, peripheral neuropathies, retinopathies and glaucoma, non-insulin dependent diabetes (such as diabetes type II), and obesity, manic depressive illness, schizophrenia, alopecia, cancers such as breast cancer, non-small cell lung carcinoma, thyroid cancer, T or B-cell leukemia and several virus-induced tumors.

A type of the pharmaceutical composition is not particularly limited, and the composition may be provided as any formulation for oral or parenteral administration. For example, the pharmaceutical composition may be formulated, for example, in the form of pharmaceutical compositions for oral administration such as granules, fine granules, powders, hard capsules, soft capsules, syrups, emulsions, suspensions, solutions and the like, or in the form of pharmaceutical compositions for parenteral administrations such as injections for intravenous, intramuscular, or subcutaneous administration, drip infusions, transdermal preparations, transmucosal preparations, nasal drops, inhalants, suppositories and the like. Injections or drip infusions may be prepared as powdery preparations such as in the form of lyophilized preparations, and may be used by dissolving just before use in an appropriate aqueous medium such as physiological saline. Sustained-release preparations such as those coated with a polymer may be directly administered intracerebrally.

Types of pharmaceutical additives used for the manufacture of the pharmaceutical composition, content ratios of the pharmaceutical additives relative to the active ingredient, and methods for preparing the pharmaceutical composition may be appropriately chosen by those skilled in the art. Inorganic or organic substances, or solid or liquid substances may be used as pharmaceutical additives. Generally, the pharmaceutical additives may be incorporated in a ratio ranging from 1% by weight to 90% by weight based on the weight of an active ingredient.

Examples of excipients used for the preparation of solid pharmaceutical compositions include, for example, lactose, sucrose, starch, talc, cellulose, dextrin, kaolin, calcium carbonate and the like. For the preparation of liquid compositions for oral administration, a conventional inert diluent such as water or a vegetable oil

may be used. The liquid composition may contain, in addition to the inert diluent, auxiliaries such as moistening agents, suspension aids, sweeteners, aromatics, colorants, and preservatives. The liquid composition may be filled in capsules made of an absorbable material such as gelatin. Examples of solvents or suspension mediums used for the preparation of compositions for parenteral administration, e.g. injections, suppositories, include water, propylene glycol, polyethylene glycol, benzyl alcohol, ethyl oleate, lecithin and the like. Examples of base materials used for suppositories include, for example, cacao butter, emulsified cacao butter, lauric lipid, witepsol.

Dose and frequency of administration of the medicament of the present invention are not particularly limited, and they may be appropriately chosen depending on conditions such as a purpose of preventive and/or therapeutic treatment, a type of a disease, the body weight or age of a patient, severity of a disease and the like. Generally, a daily dose for oral administration to an adult may be 0.01 to 1,000 mg (the weight of an active ingredient), and the dose may be administered once a day or several times a day as divided portions, or once in several days. When the medicament is used as an injection, administrations may preferably be performed continuously or intermittently in a daily dose of 0.001 to 100 mg (the weight of an active ingredient) to an adult.

Examples

The present invention will be explained more specifically with reference to examples. However, the scope of the present invention is not limited to the following examples. The compound numbers in the examples correspond to those in the table above.

Reference Example 1: Synthesis of 2-mercapto-3-methyl-6-(4-pyrimidyl)-3H-pyrimidin-4-one

A solution of ethyl 3-oxo-3-(4-pyrimidyl)propionate (34.1 g, 176 mmol), N-methyl thiourea (47.5 g, 527 mmol) and 1,8-diazabicyclo[5,4,0]-7-undecene (26.3 ml, 176 mmol) in ethanol (340 ml) was refluxed for 2 hours and the solution of methanesulfonic acid (16.9 g, 176 mmol) in water (70 ml) was added after cooling by

ice-water. The precipitate was washed with water, filtered and dried to give the title compound (30.2 g, 78%).

$^1\text{H-NMR}$ ($\text{DMSO}-d_6$) δ : 3.56(s, 3H), 6.88(s, 1H), 8.24(dd, $J=1.2, 5.4$ Hz, 2H), 9.05 (dd, $J=5.4$ Hz, 1H), 11.94(s, 1H).

Reference Example 2: Synthesis of 2-chloro-3-methyl-6-(4-pyrimidyl)-3H-pyrimidin-4-one

Phosphorous oxychloride (4.60 g, 30 mmol) was added to dimethylformamide(32 ml) and stirred for 20 min at 0°C. 2-Mercapto-3-methyl-6-(4-pyrimidyl)-3H-pyrimidine-4-one(4.40 g, 20 mmol) was added to the solution and stirred 5 min and then stirred at 70°C for 2 hours. The reaction mixture was poured into ice water, neutralized by solid potassium carbonate, and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, and evaporated under reduced pressure. Purification of the residue by silica gel chromatography (ethyl acetate) gave the title compound (1.20 g, 27%).

$^1\text{H-NMR}$ (CDCl_3) δ : 3.74(s, 3H), 7.56(s, 1H), 8.18(d, $J=5.1$ Hz, 1H), 8.92(d, $J=5.1$ Hz, 1H), 9.30(s, 1H).

MS[M+H] $^+$: 223.

Example 1: Synthesis of 2-(2-(4-fluoro-2-methoxyphenyl)piperazin-4-yl)-3-methyl-6-(4-pyrimidyl)-pyrimidin-4-one

A solution of 2-bromo-5-fluoroanisole (11.8 g, 57.6 mmol) in tetrahydrofuran (60 ml) was dropped into the magnesium (1.40 g, 57.6 mmol) in refluxed tetrahydrofuran (32 ml) containing small amount of 1,2-dibromoethane and refluxed for 15 min. After addition of tetrahydrofuran (50 ml), the solution was cooled to -78 °C and diethyl oxalate (7.41 g, 50.7 mmol) in diethyl ether (50 ml) was dropped into the solution. After stirring at the same temperature for 30 min, the solution was warmed to -10°C and 1N aqueous hydrogen chloride (50 ml) and water were added. Organic layer was extracted with diethyl ether, washed with brine and dried over magnesium sulfate. After removal of the solvent under reduced pressure, purification of the residue by silica gel column chromatography (eluent: hexane/ethyl acetate = 5/2) gave ethyl 2-(4-fluoro-2-methoxyphenyl)-2-oxoacetate

(6.80g, 59%)

$^1\text{H-NMR}$ (CDCl_3) δ : 1.40(3H, t, $J=7.1$ Hz), 3.87(3H, s), 4.89(2H, q, $J=7.1$ Hz), 6.68(1H, d, $J=10.5$ Hz), 6.77-6.81(1H, m), 7.91-7.95(1H, m).

Ethylenediamine (0.60 g, 10.0 mmol) was added to a solution of ethyl 2-(4-fluoro-2-methoxyphenyl)-2-oxoacetate (2.26 g, 10.0 mmol) in ethanol (30 ml) and refluxed 4 hr. After removal of the solvent under reduced pressure, residue was washed with ethanol-diethyl ether to give 5,6-dihydro-3-(4-fluoro-2-methoxyphenyl)pyrazinone (1.76 g, 79%).

$^1\text{H-NMR}$ (CDCl_3) δ : 3.50-3.56 (2H, m), 3.81 (3H, s), 3.88-3.92 (2H, m), 6.65(1H, d, $J=11.0$ Hz), 6.70-6.76 (1H, m), 6.89(1H, bs), 7.36-7.40(1H, m).

5,6-Dihydro-3-(4-fluoro-2-methoxyphenyl)pyrazinone was added to the solution of lithium aluminium hydride (0.46 g, 12 mmol) in diethyl ether (25 ml) and refluxed for 6 hr. Water (0.48 ml), 15% sodium hydroxide solution (0.48 ml) and again water (1.21 ml) were added to the ice-cooled solution and the precipitate was filtered and washed with dichloromethane. Combined organic layer was evaporated to give 2-(4-fluoro-2-methoxyphenyl)piperazine (0.83 g, 99%).

$^1\text{H-NMR}$ (CDCl_3) δ : 2.02(2H, s), 2.57-2.63 (1H, m), 2.80-2.89 (1H, m), 2.92-2.99 (2H, m), 3.06-3.12 (2H, m), 3.80(3H, s), 4.06 (1H, d, $J=10.0$ Hz), 6.56-6.65 (2H, m), 7.40 (1H, t, $J=7.8$ Hz).

2-Chloro-3-methyl-6-(4-pyrimidyl)-pyrimidin-4-one (223 mg, 1.0 mmol) was added to an ice-cooled solution of 2-(4-fluoro-2-methoxyphenyl)piperazine (210 mg, 1.0 mmol), triethylamine (0.15 ml, 1.1 mmol) in *N,N*-dimethylformamide (10 ml) and stirred at that temperature for 0.5 hr and then at room temperature for 3 hours. Reaction was quenched by ice-water and the filtrate was washed with water and dried to give 2-(2-(4-fluoro-2-methoxyphenyl)piperazin-4-yl)-3-methyl-6-(4-pyrimidyl)-pyrimidin-4-one (262 mg, 66%).

$^1\text{H-NMR}$ (CDCl_3) δ : 2.89-2.98 (1H, m), 3.22-3.31 (3H, m), 3.60 (3H, s), 3.62-3.71 (2H, m), 3.86 (3H, s), 4.39-4.44 (1H, m), 6.43-6.73 (2H, m), 7.33 (1H, s), 7.52-7.56 (1H, m), 8.19 (1H, d, $J=5.1$ Hz), 8.87 (1H, d, $J=5.2$ Hz), 9.28 (1H, d, $J=1.2$ Hz).

4N Hydrogen chloride in 1,4-dioxane (0.2 ml) was added to the solution of 2-(2-(4-fluoro-2-methoxyphenyl)piperazin-4-yl)-3-methyl-6-(4-pyrimidyl)-pyrimidin-4-one (238 mg, 0.6 mmol) in dichloromethane (5 ml) and stirred for 15 min. Wash

with methanol and ethyl acetate after removal of the solvent and dryness gave the title compound (223 mg, 86%).

Example 2: Synthesis of 2-(2-(4-chlorophenyl)-piperazine-4-yl)-3-methyl-6-(4-pyrimidyl)pyrimidin-4-one

Dimethyl sulfoxide (60 ml) solution of 4-chlorophenacylbromide (11.11 g, 65.9 mmol) and water (1.7 ml) were stirred. The solution was extracted with ethyl acetate 3 times and washed with water twice and brine and then dried over sodium sulfate. After removal of the solvent, the residue was washed with hexane-ethyl acetate and dried to give 4-chlorophenylglyoxal (4.43 g, 50%).

$^1\text{H-NMR}$ (CDCl_3) δ : 4.02-4.16(2H, m), 5.90-5.95(1H, m), 7.45-7.53(2H, m), 8.05-8.11(2H, m).

A methanol (10 ml) solution of ethylenediamine (1.90 g, 31.6 mmol) was added to the ice-cooled solution of 4-chlorophenylglyoxal (4.43 g, 26.3 mmol) in methanol (100 ml) and tetrahydrofuran (30 ml) and stirred for 10 min. After addition of sodium tetrahydroborate (3.26 g, 86.3 mmol), additional methanol (50 ml) was added and stirred overnight. After removal of the solvent, diluted hydrochloric acid was added and extracted with ether twice. After addition of sodium hydroxide, basic aqueous layer was extracted with dichloromethane three times and washed with brine and dried over sodium sulfate. After removal of the solvent by filtration, purification of the residue by silica gel column chromatography (eluent; dichloromethane/ethanol = 10/1 to dichloromethane/ethanol/diethylamine = 20/2/1) to give 2-(4-chlorophenyl)-piperazine (0.43 g, 9%)

$^1\text{H-NMR}$ (CDCl_3) δ : 2.67(1H, dd, $J=10.5, 12.0$ Hz), 2.87-3.03(4H, m), 3.07-3.13(1H, m), 3.77(1H, dd, $J=2.7, 10.2$ Hz), 7.27-7.36(4H, m).

Triethylamine (528 mg, 5.2 mmol) was added to a solution of 4-(chlorophenyl)piperazine (216 mg, 1.1 mmol) and 2-chloro-3-methyl-6-(4-pyrimidyl)pyrimidin-4-one and stirred at 50°C for 2 hr. Solvent was removed under reduced pressure, and 1N aqueous sodium hydroxide solution was added to the residue and extracted by dichloromethane. After washing with brine and dryness

by sodium sulfate, solvent was removed under reduced pressure, and the residue was purified using ISOLUTE(registered trade mark) SI (International Sorvent Technology, UK)(eluent; dichloromethane/ethanol = 10/1) to give the title compound (396 mg, 95 %).

The compounds in the following table were prepared in the same manner as the methods described above. The compound numbers in the following table correspond to those shown in the above-described table of preferred compounds.

Table 3

No.	NMR	MS[M+1]
A0262	(DMSO-d ₆): 3.47(3H, s), 3.48-3.66(4H, m), 3.89-4.02(2H, m), 4.98(1H, m), 7.06(1H, s), 7.35-7.59(3H, m), 7.99(1H, dd, J=7.2, 6.9Hz), 8.25(1H, dd, J=5.4, 1.2Hz), 9.01(1H, d, J=5.1Hz), 9.31(1H, s), 9.84(1H, m), 10.19(1H, m).	367
A0263	(CDCl ₃): 3.01(1H, dd, J=10.5, 12.4Hz), 3.10-3.35(3H, m), 3.57(3H, s), 3.55-3.65(2H, m), 4.05(1H, dd, J=2.4, 10.4Hz), 7.00-7.10(1H, m), 7.30(1H, s), 7.22(2H, m), 7.30-7.42(2H, m), 8.15(1H, dd, J=1.3, 5.2Hz), 8.86(1H, d, J=5.2Hz), 9.27(1H, d, J=1.0Hz).	367
A0264	2.83(1H, dd, J=11.0, 11.9 Hz), 2.93(1H, s), 2.99-3.10(3H, m), 3.45(3H, s), 3.61-3.69(2H, m), 3.95(1H, dd, J=2.1, 10.3 Hz), 6.97(1H, s), 7.19(2H, t, J=8.8 Hz), 7.48-7.56(2H, m), 8.17(1H, dd, J=1.0, 5.0 Hz), 8.99(1H, d, J=5.1 Hz), 9.29(1H, d, J=1.0 Hz)(DMSO-d ₆)	367
A0264(HCl)	3.39-3.47(2H, m), 3.45(3H, s), 3.55-3.66(2H, m), 3.86-3.96(2H, m), 4.64-4.71(1H, m), 7.05(1H, s), 7.36(2H, t, J=8.7 Hz), 7.77-7.81(2H, m), 8.23(1H, dd, J=1.2, 5.1 Hz), 9.02(1H, d, J=5.1 Hz), 9.32(1H, d, J=1.2 Hz), 9.79(1H, d, J=10.2 Hz), 10.13-10.28(1H, m)(DMSO-d ₆)	367
A0267	(CDCl ₃): 2.81(1H, dd, J=10.5, 12.6Hz), 3.15-3.40(3H, m), 3.50-3.65(4H, m), 3.65-3.80(1H, m), 4.51(1H, dd, J=2.7, 10.5Hz), 7.20-7.45(4H, m), 7.74(1H, dd, J=1.5, 7.5Hz), 8.15-8.20(1H, m), 8.85(1H, d, J=5.1Hz), 9.27(1H, s).	383
A0268	(CDCl ₃): 3.00(1H, dd, J=10.5, 12.6Hz), 3.10-3.35(3H, m), 3.50-3.70(5H, m), 4.03(1H, dd, J=2.4, 10.5Hz), 7.32(4H, m), 7.50(1H, s), 8.15(1H, dd, J=1.2, 5.1Hz), 8.87(1H, d, J=5.1Hz), 9.27(1H, d, J=1.5Hz).	383
A0269	3.40-3.50(2H, m), 3.45(3H, s), 3.53-3.65(2H, m), 3.87-3.97(2H, m), 4.68(1H, t, J=10.2 Hz), 7.05(1H, s), 7.59(2H, d, J=11.1 Hz), 7.75(2H, d, J=11.1 Hz), 8.22(1H, dd, J=1.5, 5.4 Hz), 9.02(1H, d, J=5.1 Hz), 9.31(1H, s), 9.83(1H, d, J=9.6 Hz), 10.11-10.25(1H, m)(DMSO-d ₆)	383

A0274	(DMSO-d6):3.45(3H,s), 3.40-3.70(4H,m), 3.92(2H,t,J=14.1Hz), 4.67(1H,br s), 7.06(1H,s), 7.68(2H,d,J=10.0Hz), 7.72(2H,d,J=10.0Hz), 8.22(1H,d,J=4.8Hz), 9.03(1H,d,J=4.8Hz), 9.31(1H,s), 9.88(1H,br s), 10.22(1H,br s).	427
A0289	3.38-3.57(4H, m), 3.35(3H,s), 3.89(3H,s), 3.91-3.97(2H, m), 4.84-4.94(1H, m), 7.06(1H, s), 7.08-7.15(1H, m), 7.18(1H, d, J=8.4 Hz), 7.41-7.49(1H, m), 7.68(1H, d, J=7.6 Hz), 8.25(1H, d, J=4.9 Hz), 9.04(1H, d, J=5.1 Hz), 9.32(1H, s)(DMSO)	379
A0290	(DMSO-d6) :3.40-3.75(7H,m), 3.92(2H,t,J=13.2Hz), 4.64(1H,t,J=9.1Hz), 7.00-7.10(2H,m), 7.23(1H,d,J=7.6Hz), 7.35(1H,s), 7.42(1H,t, J=7.8Hz), 8.23(1H,d,J=5.6Hz), 9.02(1H,d,J=5.2Hz), 9.32(1H,s), 9.65-9.80(1H,brd), 9.90-10.15(1H,brd).	379
A0291	(DMSO-d6): 3.42(3H, s), 3.36-3.58(4H, m), 3.79(3H, s), 3.83-3.95(2H, m), 4.61(1H, m), 7.05(1H, s), 7.07(2H, d, J=8.1Hz), 7.60(2H, d, J=8.7Hz), 8.22(1H, dd, J=5.1, 1.2Hz), 9.02(1H, d, J=5.4Hz), 9.31(1H, s), 9.58-9.74(2H, m).	379
A0294	1.31(3H, t, J=6.8 Hz), 3.44-3.59(2H, m), 3.48(3H, s), 3.87-3.97(2H, m), 4.09-4.20(2H, m), 4.80-4.91(1H, m), 7.06(1H, s), 7.09-7.17(2H, m), 7.44(1H, t, J=7.4 Hz), 7.64(1H, d, J=7.5 Hz), 8.23(1H, d, J=5.3 Hz), 9.03(1H, d, J=5.2 Hz), 9.32(1H, s), 9.49-9.60(2H, m)(DMSO-d6)	393
A0304	(DMSO-d6):3.45(3H,s), 3.64(3H,m), 3.93(3H,m), 4.78(1H,t,J=9.6Hz), 7.13(1H,s), 7.97(2H,d,J=8.7Hz), 8.01(2H,d,J=8.7Hz), 8.43(2H,d,J=6.2Hz), 8.93(2H,d,J=6.2Hz), 10.12(1H,s), 10.70(1H,s).	374
A0331	(CDCl3):2.00(4H,m), 3.05(1H,t,J=11.7Hz), 3.18-3.30(3H,m), 3.29(4H,m), 3.56(3H,s), 3.62(2H,m), 3.91(1H,d,J=8.4Hz), 6.57(2H,d,J=8.7Hz), 7.31(3H,m), 8.17(1H,dd,J=1.2,5.1Hz), 8.85(1H,d,J=5.1Hz), 9.27(1H,d,J=1.2Hz).	418
A0337	(CDCl3):3.02(1H,dd,J=10.8,12.6Hz), 3.18(8H,m), 3.56(3H,s), 3.61(1H,t,J=9.0Hz), 3.87(4H,m), 3.95(1H,dd,J=2.7,10.8Hz), 6.93(2H,d,J=8.9Hz), 7.31(1H,s), 7.36(2H,d,J=8.9Hz), 8.16(1H,dd,J=1.5,5.4Hz), 8.85(1H,d,J=5.4Hz), 9.27(1H,d,J=1.5Hz).	434
A0340	(CDCl3):2.36(3H,s), 2.59(4H,m), 3.02(1H,t,J=11.4Hz), 3.16-3.29(7H,m), 3.26(3H,s), 3.61(2H,m), 3.94(1H,d,J=8.0Hz), 6.94(2H,d,J=8.7Hz), 7.31(1H,s), 7.34(2H,d,J=8.7Hz), 8.16(1H,d,J=5.1Hz), 8.85(1H,d,J=5.1Hz), 9.27(1H,s).	447
A0361	3.39-3.50(2H, m), 3.47(3H, s), 3.61-3.73(1H, m), 3.78(3H, s), 3.83(3H, s), 3.87-3.92(3H, m), 4.92(1H, t, J=10.5 Hz), 6.99-7.11(3H, m), 7.57(1H, d, J=2.7 Hz), 8.25(1H, dd, J=1.2, 5.1 Hz), 9.03(1H, d, J=4.8 Hz), 9.31(1H, d, J=0.9 Hz), 9.78(1H, d, J=9.0 Hz), 10.21-10.38(1H, m)(DMSO-d6)	409

A0362	(DMSO-d6): 3.47(3H, s), 3.37-4.04(6H, m), 3.94(6H, s), 5.09(1H, m), 6.82(2H, d, J=8.4Hz), 7.05(1H, s), 7.45(1H, t, J=8.4Hz), 8.22(1H, m), 8.24(1H, dd, J=5.4, 1.5Hz), 9.05(1H, d, J=5.1Hz), 9.32(1H, s), 10.06(1H, m).	409
A0366	3.38-3.60(4H, m), 3.47(3H, s), 3.88-3.95(2H, m), 3.90(3H, s), 4.86-4.92(1H, m), 6.96-7.01(1H, m), 7.06(1H, s), 7.12(1H, d, J=8.8 Hz), 7.71-7.79(1H, m), 8.23-8.24(1H, m), 9.03(1H, d, J=5.1 Hz), 9.32(1H, d, J=1.2 Hz), 9.55-9.72(2H, m)(DMSO)	397
A0367/ A0368	(DMSO-d6) :3.30-3.75(7H,m), 3.80-4.00(5H,m), 4.80-5.00(1H,m), 6.93-7.00(1H,m), 7.05(1H,s), 7.11(1H,dd,J=2.4,11.4Hz), 7.84(1H,m), 8.23(1H,d,J=5.1Hz), 9.03(1H,d,J=5.1Hz), 9.31(1H,s), 9.60-9.80(1H,brd), 9.90-10.15(1H,brd).	397
A0370	3.31-3.56(3H, m), 3.45(3H, s), 3.69-3.78(1H, m), 3.90-3.99(2H, m), 3.94(3H, s), 4.95-5.03(1H, m), 6.96-7.02(1H, m), 7.03-7.09(2H, m), 7.49-7.56(1H, m), 8.24(1H, d, J=4.4 Hz), 8.51-8.69(1H, m), 9.03(1H, d, J=5.1 Hz), 9.32(1H, s), 10.55-10.67(1H, m) (DMSO)	397
A0378	2.77(1H, dd, J=10.5, 12.0 Hz), 3.18-3.30(3H, m), 3.61(3H, s), 3.64-3.71(2H, m), 3.86(3H, s), 4.37(1H, dd, J=2.1, 10.1 Hz), 6.89(1H, d, J=1.7 Hz), 6.99(1H, dd, J=1.6, 8.2 Hz), 7.32(1H, s), 7.50(1H, d, J=8.2 Hz), 8.19(1H, d, J=5.2 Hz), 8.86(1H, d, J=5.2 Hz), 9.27(1H, s)(CDCl3)	413
A0399	(CDCl3) :2.76(1H,dd,J=10.2,12.3Hz), 3.10-3.40(3H,m), 3.55-3.80(5H,m), 3.85(3H,s), 4.39(1H,dd,J=2.4,10.2Hz), 6.78(1H,d,J=8.7Hz), 7.32(1H,s), 7.39(1H,dd,J=2.7,8.7Hz), 7.72(1H,d,J=2.4Hz), 8.20(1H,dd,J=1.2,5.1Hz), 8.87(1H,d,J=5.1Hz), 9.27(1H,d,J=1.2Hz).	457
A0408	(CDCl3): 1.98-2.03(4H, m), 2.84(1H, m), 3.17-3.32(7H, m), 3.60(3H, s), 3.59-3.71(2H, m), 3.85(3H, s), 4.28(1H, d, 8.4Hz), 6.10(1H, d, J=1.8Hz), 6.18(1H, d, J=8.3Hz), 7.29(1H, s), 7.33(1H, d, J=8.4Hz), 8.21(1H, d, J=5.2Hz), 8.85(1H, d, J=5.2Hz), 9.27(1H, s).	448
A0409	(CDCl3) :1.95-2.10(4H,m), 2.95-3.10(1H,m), 3.19-3.45(7H,m), 3.59(3H,s), 3.50-3.80(2H,m), 3.80(3H,s), 4.48(1H,dd,J=2.2,10.2Hz), 6.49(1H,dd,J=3.0,8.9Hz), 6.63-6.87(2H,m), 7.32(1H,s), 8.20(1H,dd,J=1.4,5.2Hz), 8.86(2H,d,J=5.2Hz), 9.27(1H,d,J=1.1Hz).	448
A0414	(CDCl3) :3.14(2H,m), 3.22(1H,t,J=11.6Hz), 3.41(1H,t,J=11.6Hz), 3.82(2H,m), 3.83(3H,s), 3.88(3H,s), 4.58(1H,dd,J=3.1,11.0Hz), 6.51(2H,m), 7.32(1H,s), 8.19(1H,dd,J=1.5,5.3Hz), 8.86(1H,d,J=5.3Hz), 9.27(1H,d,J=1.5Hz).	415
A0423	(DMSO-d6):3.35-3.70(4H,m), 3.48(3H,s), 3.78(3H,s), 3.97(2H,m), 4.70(1H,m), 7.06(1H,t,J=7.7Hz), 7.07(1H,s), 7.15(1H,d,J=7.7Hz), 7.31(1H,d,J=7.7Hz), 7.39(1H,t,J=7.7Hz), 7.61(2H,d,J=8.1Hz), 7.70(2H,d,J=8.1Hz), 8.25(1H,d,J=4.5Hz), 9.07(1H,d,J=4.5Hz), 9.33(1H,s), 9.66(1H,br s).	455

A0425	(DMSO-d6):3.61(3H,m), 3.76(3H,s), 3.81(3H,s), 4.01(3H,m), 4.69(1H,t,J=9.9Hz), 7.05(2H,d,J=9.0Hz), 7.07(1H,s), 7.67(2H,d,J=9.0Hz), 7.76(4H,s), 8.24(1H,dd,J=1.2,5.1Hz), 9.03(1H,d,J=5.1Hz), 9.32(1H,d,J=1.2Hz), 9.79(1H,d,J=10.2Hz), 10.07(1H,s).	455
A0434	(DMSO-d6):3.30-3.70(4H,m), 3.42(3H,s), 3.96(2H,d,J=13.8Hz), 4.71(1H,t,J=11.3Hz), 7.06(1H,s), 7.33(2H,t,J=8.0Hz), 7.77(6H,m), 8.24(1H,d,J=5.4Hz), 9.03(1H,d,J=5.4Hz), 9.32(1H,s), 9.80(1H,d,J=8.7Hz), 10.03(1H,s).	443
A0442	3.43-3.59(2H, m), 3.48(3H, s), 3.63-3.75(2H, m), 3.97-4.01(2H, m), 4.80-4.86(1H, m), 7.06(1H, s), 7.60-7.64(2H, m), 7.86-7.88(1H, m), 7.95-8.00(2H, m), 8.05-8.07(1H, m), 8.24-8.27(2H, m), 9.02(1H, d, J=5.4 Hz), 9.32(1H, s), 10.01(1H, d, J=10.2 Hz), 10.30-10.41(1H, m)(DMSO-d6)	399
A0517	(CDCl3): 2.97(1H, dd, J=12.3, 10.5Hz), 3.18-3.28(5H, m), 3.58(3H, s), 3.59(1H, m), 3.77(1H, m), 4.27(1H, dd, 10.2, 2.7Hz), 4.62(2H, m), 6.89(1H, t, J=7.5Hz), 7.16(1H, m), 7.27(1H, m), 7.28(1H, s), 8.26(1H, dd, J=5.4, 1.5Hz), 8.86(1H, d, J=5.4Hz), 9.26(1H, s).	391
A0864	(DMSO-d6):3.15-3.35(1H,m), 3.38-3.50(4H,m), 3.70-4.30(9H,m), 5.00-5.20(1H,m), 7.00-7.10(2H,m), 7.10-7.20(1H,m), 7.30-7.50(6H,m), 8.15-8.20(1H,m), 8.30-8.40(1H,brd), 9.05(1H,d,J=5.1Hz), 9.31(1H,d,J=0.9Hz).	487
A1074	(CDCl3):1.80-2.40(3H, m), 3.12-3.34(4H, m), 3.39-4.20(7.6H, m), 4.50-5.07(0.6H, m), 5.30-5.60(0.7H, m), 5.72-6.05(0.1H, m), 6.52-6.80(2H, m), 6.82-7.22(1H, m), 7.28(1H, s), 8.18(1H, d,J=4.8Hz), 8.89(1H, d,J=5.1Hz), 9.28(1H, d,J=1.2Hz)	439
A1339	(CDCl3):2.50-2.62(1H,m), 2.80-2.95(1H,m), 3.02-3.20(1H,m), 3.25-3.40(1H,m), 3.50-3.74(5H,m), 3.75-3.80(1H,m), 3.85(3H,s), 6.60-6.80(2H,m), 7.30(1H,s), 7.48(1H,t,J=8.4Hz), 8.19(1H,dd,J=1.2,5.1Hz), 8.86(1H,d,J=5.1Hz), 9.27(1H,d,J=1.5Hz).	411
A1340/ A1341	(DMSO-d6):2.55(3H,d,J=3.9Hz), 3.40-3.80(3H,m), 3.45(3H,s), 3.80-4.15(6H,m), 4.85-5.15(1H,m), 6.90-7.05(1H,m), 7.05(1H,s), 7.13(1H,dd,J=2.4,11.4Hz), 8.21(1H,dd,J=1.2,5.1Hz), 9.04(1H,d,J=5.1Hz), 9.31(1H,d,J=1.2Hz), 11.50-12.20(1H,brd).	411
B013	1.31-1.46(1H, m), 1.60-1.96(3H, m), 2.17-2.30(1H, m), 2.89-3.02(2H, m), 3.41(3H, s), 3.61(1H, d, J=12.4 Hz), 3.80(1H, d, J=13.5 Hz), 3.90-4.01(2H, m), 6.89-7.01(3H, m), 6.96(1H, s), 7.27-7.32(2H, m), 8.18(1H, d, J=4.4 Hz), 8.96(1H, d, J=5.0 Hz), 9.28(1H, s)(DMSO-d6)	378

B014	1.33-1.49(1H, m), 1.60-1.93(3H, m), 2.20-2.32(1H, m), 2.89-3.04(2H, m), 3.41(3H, s), 3.63(1H, d, J=13.3 Hz), 3.82(1H, d, J=11.1 Hz), 4.22-4.37(2H, m), 6.95(1H, s), 7.51-7.56(2H, m), 7.65-7.70(1H, m), 8.00-8.03(2H, m), 8.17(1H, dd, J=1.1, 5.1 Hz), 8.87(1H, d, J=5.1 Hz), 9.28(1H, d, J=1.0 Hz)(DMSO-d6)	406
B048	(CDCl3): 1.93-2.07(3H, m), 2.38(1H, m), 3.09(1H, m), 3.46(1H, m), 3.57(3H, s), 3.61-3.70(2H, m), 4.05(1H, m), 7.26-7.34(2H, m), 7.59-7.61(2H, m), 7.76(1H, m), 8.16(1H, m), 8.83(1H, m), 9.27(1H, s).	389
B049	(CDCl3): 1.92-2.08(3H, m), 2.36(1H, m), 3.11(1H, m), 3.44(1H, dd, J=12.9, 10.8Hz), 3.58(3H, s), 3.61-3.70(2H, m), 4.06(1H, m), 7.11(1H, m), 7.28-7.33(2H, m), 7.70(1H, dd, J=8.7, 4.8Hz), 8.15(1H, m), 8.86(1H, d, J=5.4Hz), 9.28(1H, s).	407
B050	1.93-2.11(3H, m), 2.33-2.45(1H, m), 3.08-3.16(1H, m), 3.46(1H, dd, J=11.4, 12.9 Hz), 3.59(3H, s), 3.62-3.71(2H, m), 4.06(1H, d, J=12.6 Hz), 7.32-7.37(1H, m), 7.32(1H, s), 7.57-7.64(2H, m), 7.75(1H, d, J=8.1 Hz), 8.16(1H, dd, J=1.2, 5.4 Hz), 8.84(1H, d, J=4.8 Hz), 9.28(1H, d, J=0.9 Hz)(CDCl3)	389
B051	1.91-2.11(3H, m), 2.35-2.43(1H, m), 3.08-3.16(1H, m), 3.42-3.50(1H, m), 3.59(3H, s), 3.62-3.71(2H, m), 4.05(1H, d, J=11.1 Hz), 7.32(1H, s), 7.33-7.37(1H, m), 7.57-7.65(2H, m), 7.75(1H, d, J=7.8 Hz), 8.16(1H, d, J=5.7 Hz), 8.84(1H, d, J=5.4 Hz), 9.28(1H, d, J=1.2 Hz)(CDCl3)	389
B130	1.78-1.96(4H, m), 2.73-2.90(1H, m), 3.02-3.09(2H, m), 3.46(3H, s), 3.84(2H, d, J=12.6 Hz), 6.98(1H, s), 7.11-7.17(2H, m), 7.33-7.38(2H, m), 8.25(1H, d, J=5.1 Hz), 9.01(1H, d, J=4.8 Hz), 9.30(1H, s)(DMSO-d6)	366
B157	1.90-2.05(2H, m), 2.18-2.35(2H, m), 2.92-3.09(1H, m), 3.10-3.23(2H, m), 3.58(3H, s), 3.72-3.83(2H, m), 6.95-7.07(1H, m), 7.22(1H, dd, J=2.2, 9.0Hz), 7.34(1H, s), 7.46(1H, s), 7.48-7.55(1H, m), 8.20(1H, d, J=5.3Hz), 8.88(1H, d, J=5.2Hz), 9.29(1H, s)(CDCl3)	406
B158	1.91-2.04(2H, m), 2.23(2H, d, J=8.9Hz), 2.44(3H, s), 2.97-3.11(1H, m), 3.16(2H, dd, J=11.1, 12.4Hz), 3.58(3H, s), 3.77(2H, d, J=13.0Hz), 7.12(1H, d, J=8.5Hz), 7.36-7.41(4H, m), 8.20(1H, d, J=5.3Hz), 8.87(1H, d, J=4.8Hz), 9.28(1H, s) (CDCl3)	402
B159	1.93-2.05(2H, m), 2.23(2H, d, J=12.6Hz), 3.19(3H, m), 3.58(3H, s), 3.81(2H, d, J=13.2Hz), 7.12-7.16(1H, m), 7.26(1H, s), 7.34(1H, s), 7.56(1H, dd, J=2.4, 8.7Hz), 7.77-7.76(1H, m), 8.20(1H, dd, J=1.2, 5.1Hz), 8.87(1H, d, J=5.1Hz), 9.29(1H, s) (CDCl3)	422

B160	2.01-2.22(5H, m), 3.20(2H, dd, J=1.4, 11.7Hz), 3.47(3H, s), 3.84(2H, d, J=13.2Hz), 6.99(1H, s), 7.32(1H, m), 7.72(1H, dd, J=2.1, 9.0Hz), 8.09(1H, dd, J=2.7, 9.1Hz), 8.27(1H, m), 9.01(1H, d, J=5.1Hz), 9.31(1H, d, J=1.5Hz) (DMSO-d6)	407
B162	2.13-2.43(4H, m), 3.10-3.38(3H, m), 3.57(3H, s), 3.65-3.83(2H, m), 7.30-7.40(3H, m), 7.45-7.59(1H, m), 7.62-7.80(1H, m), 8.10-8.22(1H, m), 8.88(1H, d, J=5.1Hz), 9.28(1H, s) (CDCl3)	389
B193	2.22-2.39(4H, m), 3.21-3.35(2H, m), 3.48(3H, s), 3.90(2H, d, J=13.5 Hz), 7.03(1H, s), 7.38-7.43(1H, m), 7.46-7.51(2H, m), 7.59-7.66(2H, m), 8.28(1H, d, J=5.0 Hz), 9.01(1H, d, J=5.0 Hz), 9.30(1H, s) (DMSO-d6)	373

Test Example: Inhibitory activity of the medicament of the present invention against P-GS1 phosphorylation by bovine cerebral TPK1

A mixture containing 100 mM MES-sodium hydroxide (pH 6.5), 1 mM magnesium acetate, 0.5 mM EGTA, 5 mM β -mercaptoethanol, 0.02% Tween 20, 10% glycerol, 12 μ g/ml P-GS1, 41.7 μ M [γ - 32 P] ATP (68 kBq/ml), bovine cerebral TPK1 and a compound shown in Table (a final mixture contained 1.7% DMSO deriving from a solution of a test compound prepared in the presence of 10% DMSO) was used as a reaction system. The phosphorylation was started by adding ATP, and the reaction was conducted at 25°C for 2 hours, and then stopped by adding 21% perchloric acid on ice cooling. The reaction mixture was centrifuged at 12,000 rpm for 5 minutes and adsorbed on P81 paper (Whatmann), and then the paper was washed four times with 75 mM phosphoric acid, three times with water and once with acetone. The paper was dried, and the residual radioactivity was measured using a liquid scintillation counter. The results are shown in the table below. The test compound markedly inhibited the P-GS1 phosphorylation by TPK1. The results strongly suggest that the medicaments of the present invention inhibit the TPK1 activity, thereby suppress the A β neurotoxicity and the PHF formation, and that the medicaments of the present invention are effective for preventive and/or

therapeutic treatment of Alzheimer disease and the above-mentioned diseases.

Table 4

Compound No.	IC ₅₀
A0262	8.2nM
A0263	12nM
A0264	8.6nM
A0264(HCl)	7.9nM
A0267	2.6 nM
A0268	1.1 nM
A0269	1.7nM
A0274	8.1nM
A0289	0.0018 μ M
A0290	6.7nM
A0291	3.5nM
A0294	20nM
A0304	7.4 nM
A0331	10 nM
A0337	7.4 nM
A0340	1.2 nM
A0361	0.82nM
A0362	1.5nM
A0366	0.00072 μ M
A0367 A0368	44nM
A0367 A0368	0.25nM
A0370	1.4nM
A0378	1.0 nM
A0399	0.71 nM
A0408	0.77nM
A0409	1.8 nM
A0414	1.7nM
A0423	15 nM
A0425	2.4 nM
A0434	3.4nM
A0442	2.5nM
A0517	1.5 nM
A0864	216 nM
A1074	1503 nM
A1339	26nM
A1340 A1341	374nM
A1340 A1341	34nM
B013	0.015 μ M
B014	0.0296 μ M

B048	0.00063 μ M
B049	0.0040 μ M
B050	0.00066 μ M
B051	0.0046 μ M
B130	0.036 μ M
B157	0.014 μ M
B162	0.0058 μ M
B193	0.14 μ M

Formulation Example

(1) Tablets

The ingredients below were mixed by an ordinary method and compressed by using a conventional apparatus.

Compound of Example 1	30 mg
Crystalline cellulose	60 mg
Corn starch	100 mg
Lactose	200 mg
Magnesium stearate	4 mg

(2) Soft capsules

The ingredients below were mixed by an ordinary method and filled in soft capsules.

Compound of Example 1	30 mg
Olive oil	300 mg
Lecithin	20 mg

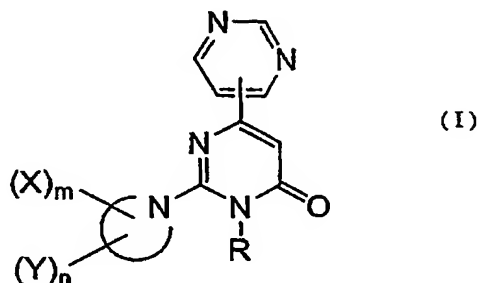
Effect of Invention

The compounds of the present invention have TPK1 inhibitory activity and are useful as an active ingredient of a medicament for preventive and/or therapeutic treatment of diseases caused by abnormal advance of TPK1 such as neurodegenerative diseases (e.g. Alzheimer disease) and the above-mentioned diseases.

【書類名】 外国語要約書

ABSTRACT

1. A pyrimidone derivative having tau protein kinase 1 inhibitory activity which is represented by formula (I) or a salt thereof, or a solvate thereof or a hydrate thereof:



wherein R represents a C₁-C₁₂ alkyl group ;
the ring of:



represents piperazine ring or piperidine ring; each X independently represents a C₁-C₈ alkyl group, an optionally partially hydrogenated C₆-C₁₀ aryl ring, an indan ring or the like; m represents an integer of 1 to 3; each Y independently represents a halogen atom, a hydroxy group, a cyano group or the like; when X and Y or two Y groups are attached on the same carbon atom, they may combine to each other to form a C₂-C₆ alkylene group.

【書類名】 翻訳文提出書
【整理番号】 A31199M
【提出日】 平成15年 5月26日
【あて先】 特許庁長官殿

【出願の表示】

【出願番号】 特願2003-126022

【特許出願人】

【識別番号】 000006725

【氏名又は名称】 三菱ウェルファーマ株式会社

【特許出願人】

【識別番号】 399050909

【氏名又は名称】 サノフィーサンテラボ

【代理人】

【識別番号】 110000109

【氏名又は名称】 特許業務法人特許事務所サイクス

【代表者】 今村 正純

【確認事項】 本書に添付した翻訳文は、特願 2 0 0 3 - 1 2 6 0 2 2 の正確な日本語への翻訳文であり、当該特許出願に記載されていない事項が本書に添付した翻訳文に記載されている場合には、当該出願が拒絶又は無効となる可能性がある」と承知していることを申し述べる。

【提出物件の目録】

【物件名】 外国語明細書の翻訳文 1

【物件名】 外国語要約書の翻訳文 1

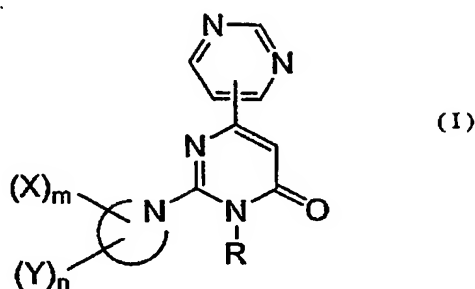
【書類名】 明細書

【発明の名称】 3-置換-4-ピリミドン誘導体

【特許請求の範囲】

【請求項1】 下記式(I)：

【化1】



【式中、Rは、置換されていてもよいC₁～C₁₂のアルキル基を示し；

【化2】



はピペラジン環またはピペリジン環を示し；

Xはそれぞれ独立して、置換されていてもよいC₁～C₈のアルキル基、一部が水素化されていてもよい置換されていてもよいC₆～C₁₀のアリール環、置換されていてもよいインダン環、酸素原子、硫黄原子、及び窒素原子から成る群から選ばれる1～4個のヘテロ原子を有し、かつ全部で5～10個の環構成原子を有する、置換されていることもあるヘテロ環、又はX¹—CO—(X¹は置換されていてもよいC₆～C₁₀のアリール環、又は置換されていてもよいC₁～C₈のアルキル基を示す。)を示し；

mは1ないし3のいずれかの整数を示し；

Yはそれぞれ独立して、ハロゲン原子、水酸基、シアノ基、置換されていてもよいC₁～C₆のアルキル基、Y¹—CO—(Y¹は置換されていてもよいC₆～C₁₀のアリール環、又は置換されていてもよいC₁～C₈のアルキル基を示す。)、又はY²—O—CO—(Y²は置換されていてもよいC₁～C₈のアルキル基を示す。)を示し；

nは0ないし8のいずれかの整数を示し；

XとY、又は二つのY基が同じ炭素に結合している場合には、それらはそれぞれ結合してC₂～C₆のアルキレン基を形成してもよく；

および、mが1のとき、nは0で、XはX¹-CO-であり、そのとき：

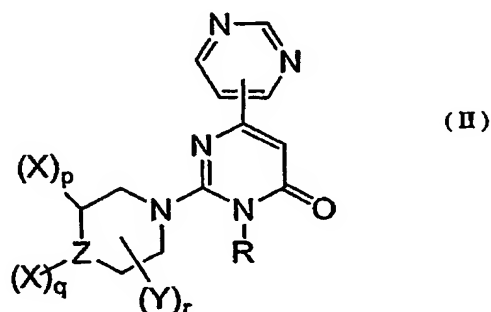
(1) Xは無置換の1-ピペラジニル基の3位に結合していず、又は、4-アルキル-1-ピペラジニル基の3位に結合していず、又は

(2) Xは無置換の1-ピペリジニル基の3位又は4位に結合していない。}

で表されるピリミドン誘導体若しくはその塩、又はそれらの溶媒和物若しくはそれらの水和物。

【請求項2】 下記式 (I I)

【化3】



{式中、R、X、およびYは請求項1と同義であり；

pは0又は1であり；qは0または1であり；rは0ないし6のいずれかの整数であり；p+qは1または2であり；ZはNまたはC Z¹ (Z¹は水素原子またはYを示す。)を示す。}

を有する請求項1に記載のピリミドン誘導体若しくはその塩、又はそれらの溶媒和物若しくはそれらの水和物。

【請求項3】 RがC₃～C₈のシクロアルキル基で置換されていてもよいC₁～C₃のアルキル基である請求項2に記載のピリミドン誘導体若しくはその塩、又はそれらの溶媒和物若しくはそれらの水和物。

【請求項4】 Rがメチル基またはエチル基であり；Yがピペラジン環又ピペリジン環の3位、4位又は5位にあり；p+qが1であり；およびrが0ないし3のいずれかの整数である請求項3に記載のピリミドン誘導体若しくはその塩、又はそれらの溶媒和物若しくはそれらの水和物。

【請求項5】 Xが置換されていてもよいC₁～C₈のアルキル基、又は置換されていてもよいC₆～C₁₀のアリール環であり；Yが置換されていてもよいC₁～C₆のアルキル基であり；pが1であり；qが0であり；rが0ないし3のいずれかの整数であり；ZがN又はCHである請求項4に記載のピリミドン誘導体若しくはその塩、又はそれらの溶媒和物若しくはそれらの水和物。

【請求項6】 Xが置換されていてもよいベンゼン環、置換されていてもよいベンジル基であり；Yが置換されていてもよいメチル基であり；ZがNであり；およびrが0又は1である請求項5に記載のピリミドン誘導体若しくはその塩、又はそれらの溶媒和物若しくはそれらの水和物。

【請求項7】 Xが置換されていてもよいベンゼン環、置換されていてもよいベンジル基、置換されていてもよいベンゾイル基、又は置換されていてもよいベンゾイソチアゾール環であり；Yが置換されていてもよいメチル基であり；ZがNであり、およびpが0である請求項4に記載のピリミドン誘導体若しくはその塩、又はそれらの溶媒和物若しくはそれらの水和物。

【請求項8】 Xが置換されていてもよいベンゼン環で置換されたC₁～C₈のアルキル基、又は置換されていてもよいベンゼン環であり；Yが水酸基、シアノ基、又はY¹-CO-（Y¹はC₁～C₈のアルキル基である。）であり；ZがCHまたはC-Yであり、及びrが0又は1である請求項4に記載のピリミドン誘導体若しくはその塩、又はそれらの溶媒和物若しくはそれらの水和物。

【請求項9】 Xが置換されていてもよいベンジル基、又は置換されていてもよいベンゼン環であり、又は置換されていてもよいベンゼン環であり；Yが水酸基、シアノ基、又はアセチル基であり；ZがCHまたはC-Yであり、及びrが0又は1である請求項8に記載のピリミドン誘導体若しくはその塩、又はそれらの溶媒和物若しくはそれらの水和物。

【請求項10】 2-（3-フェニルピペラジン-1-イル）-3-メチル-6-（4-ピリミジル）-3H-ピリミジン-4-オン；
2-（3-（4-フルオロフェニル）ピペラジン-1-イル）-3-メチル-6-（4-ピリミジル）-3H-ピリミジン-4-オン；
2-（3-（3-フルオロフェニル）ピペラジン-1-イル）-3-メチル-6-

- (4-ピリミジル) — 3H-ピリミジン-4-オン;
- 2- (3- (2-フルオロフェニル) ピペラジン-1-イル) — 3-メチル-6-
— (4-ピリミジル) — 3H-ピリミジン-4-オン;
- 2- (3- (4-クロロフェニル) ピペラジン-1-イル) — 3-メチル-6-
(4-ピリミジル) — 3H-ピリミジン-4-オン;
- 2- (3- (3-クロロフェニル) ピペラジン-1-イル) — 3-メチル-6-
(4-ピリミジル) — 3H-ピリミジン-4-オン;
- 2- (3- (2-クロロフェニル) ピペラジン-1-イル) — 3-メチル-6-
(4-ピリミジル) — 3H-ピリミジン-4-オン;
- 2- (3- (4-ブロモフェニル) ピペラジン-1-イル) — 3-メチル-6-
(4-ピリミジル) — 3H-ピリミジン-4-オン;
- 2- (3- (3-ブロモフェニル) ピペラジン-1-イル) — 3-メチル-6-
(4-ピリミジル) — 3H-ピリミジン-4-オン;
- 2- (3- (2-ブロモフェニル) ピペラジン-1-イル) — 3-メチル-6-
(4-ピリミジル) — 3H-ピリミジン-4-オン;
- 2- (3- (4-シアノフェニル) ピペラジン-1-イル) — 3-メチル-6-
(4-ピリミジル) — 3H-ピリミジン-4-オン;
- 2- (3- (3-シアノフェニル) ピペラジン-1-イル) — 3-メチル-6-
(4-ピリミジル) — 3H-ピリミジン-4-オン;
- 2- (3- (2-シアノフェニル) ピペラジン-1-イル) — 3-メチル-6-
(4-ピリミジル) — 3H-ピリミジン-4-オン;
- 2- (3- (4-メトキシフェニル) ピペラジン-1-イル) — 3-メチル-6-
(4-ピリミジル) — 3H-ピリミジン-4-オン;
- 2- (3- (3-メトキシフェニル) ピペラジン-1-イル) — 3-メチル-6-
(4-ピリミジル) — 3H-ピリミジン-4-オン;
- 2- (3- (2-メトキシフェニル) ピペラジン-1-イル) — 3-メチル-6-
(4-ピリミジル) — 3H-ピリミジン-4-オン;
- 2- (3- (2-エトキシフェニル) ピペラジン-1-イル) — 3-メチル-6-
(4-ピリミジル) — 3H-ピリミジン-4-オン;

- 2- (3- (6-フルオロ-2-メトキシフェニル) ピペラジン-1-イル) -
3-メチル-6- (4-ピリミジル) -3H-ピリミジン-4-オン;
- 2- (3- (5-フルオロ-2-メトキシフェニル) ピペラジン-1-イル) -
3-メチル-6- (4-ピリミジル) -3H-ピリミジン-4-オン;
- 2- (3- (4-フルオロ-2-メトキシフェニル) ピペラジン-1-イル) -
3-メチル-6- (4-ピリミジル) -3H-ピリミジン-4-オン;
- (S) -2- (3- (4-フルオロ-2-メトキシフェニル) ピペラジン-1-
イル) -3-メチル-6- (4-ピリミジル) -3H-ピリミジン-4-オン;
- (R) -2- (3- (4-フルオロ-2-メトキシフェニル) ピペラジン-1-
イル) -3-メチル-6- (4-ピリミジル) -3H-ピリミジン-4-オン;
- 2- (3- (4-クロロ-2-メトキシフェニル) ピペラジン-1-イル) -3-
メチル-6- (4-ピリミジル) -3H-ピリミジン-4-オン;
- 2- (3- (5-ブromo-2-メトキシフェニル) ピペラジン-1-イル) -3-
メチル-6- (4-ピリミジル) -3H-ピリミジン-4-オン;
- 2- (3- (2, 6-ジクロロフェニル) ピペラジン-1-イル) -3-メチル-
6- (4-ピリミジル) -3H-ピリミジン-4-オン;
- 2- (3- (2, 4-ジメトキシフェニル) ピペラジン-1-イル) -3-メチル-
6- (4-ピリミジル) -3H-ピリミジン-4-オン;
- 2- (3- (3, 4-ジメトキシフェニル) ピペラジン-1-イル) -3-メチル-
6- (4-ピリミジル) -3H-ピリミジン-4-オン;
- 2- (3- (2, 5-ジメトキシフェニル) ピペラジン-1-イル) -3-メチル-
6- (4-ピリミジル) -3H-ピリミジン-4-オン;
- 2- (3- (2, 6-ジメトキシフェニル) ピペラジン-1-イル) -3-メチル-
6- (4-ピリミジル) -3H-ピリミジン-4-オン;
- 2- (3- (2, 4-ジフルオロ-6-メトキシフェニル) ピペラジン-1-イル) -
3-メチル-6- (4-ピリミジル) -3H-ピリミジン-4-オン;
- 2- (3- (1-ナフチル) ピペラジン-1-イル) -3-メチル-6- (4-
ピリミジル) -3H-ピリミジン-4-オン;
- 2- (3- (2-ナフチル) ピペラジン-1-イル) -3-メチル-6- (4-

ピリミジル) - 3H-ピリミジン-4-オン;

2 - (3 - (2, 3-ジヒドロベンゾフラン-7-イル) ピペラジン-1-イル) - 3-メチル-6 - (4-ピリミジル) - 3H-ピリミジン-4-オン;

2 - (3 - (ベンゾフラン-2-イル) ピペラジン-1-イル) - 3-メチル-6 - (4-ピリミジル) - 3H-ピリミジン-4-オン;

2 - (3 - (4 - (ピロリジン-1-イル-メチル) フェニル) ピペラジン-1-イル) - 3-メチル-6 - (4-ピリミジル) - 3H-ピリミジン-4-オン;
;

2 - (3 - (4 - (ピロリジン-1-イル) フェニル) ピペラジン-1-イル) - 3-メチル-6 - (4-ピリミジル) - 3H-ピリミジン-4-オン;

2 - (3 - (2-メトキシ-4 - (ピロリジン-1-イル) フェニル) ピペラジン-1-イル) - 3-メチル-6 - (4-ピリミジル) - 3H-ピリミジン-4-オン;

2 - (3 - (2-メトキシ-5 - (ピロリジン-1-イル) フェニル) ピペラジン-1-イル) - 3-メチル-6 - (4-ピリミジル) - 3H-ピリミジン-4-オン;

2 - (3 - (4 - (フェニル) フェニル) ピペラジン-1-イル) - 3-メチル-6 - (4-ピリミジル) - 3H-ピリミジン-4-オン;

2 - (3 - (4 - (4-フルオロフェニル) フェニル) ピペラジン-1-イル) - 3-メチル-6 - (4-ピリミジル) - 3H-ピリミジン-4-オン;

2 - (3 - (4 - (4-メトキシフェニル) フェニル) ピペラジン-1-イル) - 3-メチル-6 - (4-ピリミジル) - 3H-ピリミジン-4-オン;

2 - (3 - (4 - (2-メトキシフェニル) フェニル) ピペラジン-1-イル) - 3-メチル-6 - (4-ピリミジル) - 3H-ピリミジン-4-オン;

2 - (3 - (4 - (モルホリン-4-イル) フェニル) ピペラジン-1-イル) - 3-メチル-6 - (4-ピリミジル) - 3H-ピリミジン-4-オン;

2 - (3 - (4 - (4-メチルピペラジン-1-イル) フェニル) ピペラジン-1-イル) - 3-メチル-6 - (4-ピリミジル) - 3H-ピリミジン-4-オン;
;

2 - (3 - (4 - フルオロ - 2 - メトキシフェニル) - 4 - メチルピペラジン - 1 - イル) - 3 - メチル - 6 - (4 - ピリミジル) - 3 H - ピリミジン - 4 - オン;

(S) - 2 - (3 - (4 - フルオロ - 2 - メトキシフェニル) - 4 - メチルピペラジン - 1 - イル) - 3 - メチル - 6 - (4 - ピリミジル) - 3 H - ピリミジン - 4 - オン;

(R) - 2 - (3 - (4 - フルオロ - 2 - メトキシフェニル) - 4 - メチルピペラジン - 1 - イル) - 3 - メチル - 6 - (4 - ピリミジル) - 3 H - ピリミジン - 4 - オン;

2 - (4 - アセチル - 3 - (4 - フルオロ - 2 - メトキシフェニル) ピペラジン - 1 - イル) - 3 - メチル - 6 - (4 - ピリミジル) - 3 H - ピリミジン - 4 - オン;

2 - (4 - ベンジル - 3 - (4 - フルオロ - 2 - メトキシフェニル) ピペラジン - 1 - イル) - 3 - メチル - 6 - (4 - ピリミジル) - 3 H - ピリミジン - 4 - オン;

2 - (4 - (4 - フルオロフェニル) ピペリジン - 1 - イル) - 3 - メチル - 6 - (4 - ピリミジル) - 3 H - ピリミジン - 4 - オン;

2 - (4 - シアノ - 4 - フェニルピペリジン - 1 - イル) - 3 - メチル - 6 - (4 - ピリミジル) - 3 H - ピリミジン - 4 - オン;

2 - (4 - (6 - フルオロベンゾフラン - 3 - イル) ピペリジン - 1 - イル) - 3 - メチル - 6 - (4 - ピリミジル) - 3 H - ピリミジン - 4 - オン;

2 - (3 - (ベンゾイソキサゾール - 3 - イル) ピペリジン - 1 - イル) - 3 - メチル - 6 - (4 - ピリミジル) - 3 H - ピリミジン - 4 - オン;

(S) - 2 - (3 - (ベンゾイソキサゾール - 3 - イル) ピペリジン - 1 - イル) - 3 - メチル - 6 - (4 - ピリミジル) - 3 H - ピリミジン - 4 - オン;

(R) - 2 - (3 - (ベンゾイソキサゾール - 3 - イル) ピペリジン - 1 - イル) - 3 - メチル - 6 - (4 - ピリミジル) - 3 H - ピリミジン - 4 - オン;

2 - (3 - (6 - フルオロベンゾイソキサゾール - 3 - イル) ピペリジン - 1 - イル) - 3 - メチル - 6 - (4 - ピリミジル) - 3 H - ピリミジン - 4 - オン;

2- (4- (6-フルオロベンゾイソキサゾール-3-イル) ピペリジン-1-イル) -3-メチル-6- (4-ピリミジル) -3H-ピリミジン-4-オン;
2- (4- (5-メチルベンゾフラン-3-イル) ピペリジン-1-イル) -3-メチル-6- (4-ピリミジル) -3H-ピリミジン-4-オン;
2- (4- (6-フルオロベンゾチオフエン-3-イル) ピペリジン-1-イル) -3-メチル-6- (4-ピリミジル) -3H-ピリミジン-4-オンから成る群から選ばれるピリミドン誘導体若しくはその塩、又はそれらの溶媒和物若しくはそれらの水和物。

【請求項 11】 請求項 1 に記載の式 (I) で表されるピリミドン誘導体若しくはその塩、又はそれらの溶媒和物若しくはそれらの水和物から成る群より選ばれる物質を有効成分として含有する医薬。

【請求項 12】 請求項 1 に記載の式 (I) で表されるピリミドン誘導体若しくはその塩、又はそれらの溶媒和物若しくはそれらの水和物から成る群からより選ばれるタウプロテインキナーゼ 1 の阻害剤。

【請求項 13】 タウプロテインキナーゼ 1 の機能亢進に起因する疾患の予防及び／又は治療に用いる、請求項 11 に記載の医薬。

【請求項 14】 神経変性疾患の予防及び／又は治療のための、請求項 11 に記載の医薬。

【請求項 15】 前記疾患が、アルツハイマー病、虚血性脳血管障害、ダウン症候群、脳アミロイドアンギオパチーによる脳出血、進行性核上麻痺、亜急性硬化性全脳炎性パーキンソン症候群、脳炎後パーキンソン症候群、拳闘家脳症、グアム・パーキンソン痴呆複合症、レビー小体病、ピック病、皮質底部変性症、前頭側頭性痴呆、血管性痴呆、外傷性損傷、脳及び脊髄損傷、末梢性ニューロパシー、網膜症、及び緑内障から成る群から選ばれる、請求項 14 に記載の医薬。

【請求項 16】 前記疾患が、インスリン非依存性糖尿病、肥満症、躁鬱病、精神分裂病、脱毛症、乳癌、非小細胞肺癌、甲状腺癌、T 又は B 細胞白血病、及びウイルス誘導性腫瘍から成る群から選ばれる、請求項 11 に記載の医薬。

【発明の詳細な説明】

【0001】

【発明の属する技術分野】

本発明は、神経変性疾患（例えばアルツハイマー病）などの、タウプロテインキナーゼ1の異常亢進に主に起因する疾患の予防及び／又は治療のための医薬の有効成分として有用な化合物に関する。

【0002】**【従来の技術】**

アルツハイマー病は進行性の老年期痴呆であり、神経細胞の変性及び神経細胞数の減少による脳の萎縮が顕著に認められる。病理学的には、脳内に多数の老人斑と神経原線維変化が認められる。患者数は、高齢人口の増加と共に増大し、該疾患は深刻な社会問題を起こしている。この疾患の原因については諸説あるものの未だ不明であり、早期の解明が望まれている。

【0003】

アルツハイマー病に特徴的な2つの病理変化の出現程度は、知的機能障害の程度とよく相関することが知られている。そこで、この2つの病理変化の構成成分に関する分子レベルの研究を通して、該疾患の病因を明らかにしようとする研究が1980年代前半より行われてきた。老人斑は細胞外に蓄積するもので、その主構成成分がアミロイド β 蛋白（本明細書において以下「A β 」と略す）であることが解明されている（*Biochem. Biophys. Res. Commun.*, 120, 855（1984）；*EMBOJ*, 4, 2757（1985）；*Proc. Natl. Acad. Sci. USA*, 82, 4245（1985））。また、もう1つの病理変化である神経原線維変化はペアードーヘリカルフィラメント（*Paired Helical Filament*：本明細書において以下「PHF」と略す）と呼ばれる二重螺旋状の線維状物質が細胞内に蓄積してくるものであり、その主構成成分は脳に特異的な微小管付随蛋白質の一種であるタウ蛋白質であることが明らかにされている（*Proc. Natl. Acad. Sci. USA*, 85, 4506（1988）；*Neuron*, 1, 827（1988））。

【0004】

さらに遺伝学的研究より、家族性アルツハイマー病の原因遺伝子としてプレセ

ニリン1及び2が見つかり (Nature, 375, 754 (1995); Science, 269, 973 (1995); Nature, 376, 775 (1995))、プレセニリン1及び2の変異体が存在するとA β の分泌が促進することが明らかとなった (Neuron, 17, 1005 (1996); Proc. Natl. Acad. Sci. USA, 94, 2025 (1997))。これらの結果からアルツハイマー病は、何らかの原因でA β が異常に蓄積、凝集し、これがPHFの形成と連動して神経細胞の死を招くものと考えられている。また、虚血性脳血管障害に伴う神経細胞死の発生過程において、細胞外へのグルタミン酸流出、及びそれに応答するグルタミン酸受容体の活性化が重要な因子になると考えられる (最新医学, 49, 1506 (1994))。

【0005】

グルタミン酸受容体の一種であるAMPA受容体を刺激するカイニン酸処置によってA β の前駆体であるアミロイド前駆体蛋白 (amyloid precursor protein: 本明細書において以下「APP」と略す) のmRNAが増加すること (Society for Neuroscience Abstracts, 17, 1445 (1991))、APPの代謝が亢進すること (The Journal of Neuroscience, 10, 2400 (1990)) が報告されており、A β の蓄積が虚血性脳血管障害による細胞死に関与していることが強く示唆される。A β が異常に蓄積、凝集する他の疾患としては、例えば、ダウン症候群、孤発性脳アミロイドアンギオパチーによる脳出血、及びレビー小体病等を挙げることができる (神経進歩, 34, 343 (1990); 蛋白質・核酸・酵素, 41, 1476 (1996))。またPHF蓄積による神経原線維変化を示す疾患としては、進行性核上麻痺、亜急性硬化性全脳炎性パーキンソン症候群、脳炎後パーキンソン症候群、拳闘家脳症、グアム・パーキンソン痴呆複合症及びレビー小体病等を挙げることができる (蛋白質・核酸・酵素, 36, 2 (1991); 医学のあゆみ, 158, 511 (1991); 蛋白質・核酸・酵素, 41, 1476 (1996))。

【0006】

タウ蛋白質は、SDS-ポリアクリルアミドゲル電気泳動で分子量48-65

KDaに数本のバンドを形成する一群の近縁蛋白質であり、微小管の形成を促進する。アルツハイマー病脳のPHF中に組み込まれたタウ蛋白質は通常のタウ蛋白質に比べて異常にリン酸化されていることが証明されてきている(J. Biochem., 99, 1807 (1986); Proc. Natl. Acad. Sci. USA, 83, 4913 (1986))。この異常なリン酸化を触媒する酵素が単離され、タウプロテインキナーゼ1(本明細書において以下、「TPK1」と略す)と命名され、その理化学的性質が解明されている(生化学, 64, 308 (1992); J. Biol. Chem., 267, 10897 (1992))。更に、TPK1の部分アミノ酸配列に基づいてラット大脳皮質cDNAライブラリーからラットTPK1のcDNAがクローニングされ、そのヌクレオチド配列が決定されると共にアミノ酸配列が推定された(特開平6-239893号公報)。その結果、このラットTPK1の1次構造がラットGSK-3 β (グリコーゲンシンターゼキナーゼ3 β)として知られる酵素の1次構造と一致することが確認されている(FEBS Lett., 325, 167 (1993))。

【0007】

老人斑の主構成成分であるA β には神経毒性があることが報告されている(Science, 250, 279 (1990))。しかしながら、なぜA β が細胞を死に至らしめるのかについては諸説あり、統一された見解は得られていない。高島らはラット胎児の海馬初代培養系にA β を処理すると細胞死が起こることを確認した後、A β 処理によりTPK1活性が増加すること、及びA β による細胞死をTPK1のアンチセンスが阻止することを発見した(Proc. Natl. Acad. Sci. USA, 90, 7789 (1993); 特開平6-329551号公報)。

【0008】

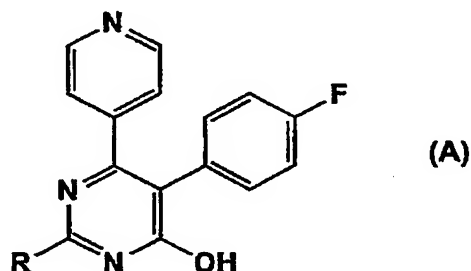
以上のことから、TPK1活性を阻害する化合物は、A β の神経毒性及びPHFの形成を抑え、アルツハイマー病における神経細胞死を阻止し、病気の進行を阻止あるいは遅らせることができる可能性がある。また、同様にA β の細胞毒性を抑えることにより、虚血性脳血管障害、ダウン症候群、脳アミロイドアンギオ

パチー、レビー小体病による脳出血等の治療剤となる可能性がある。更に、進行性核上麻痺、亜急性硬化性全脳炎性パーキンソン症候群、脳炎後パーキンソン症候群、拳闘家脳症、グアム・パーキンソン痴呆複合症、レビー小体病、ピック病、皮質底部変性症、前頭側頭性痴呆、血管性痴呆、急性発作及び外傷性損傷、脳及び脊髄損傷、末梢性ニューロパシー、網膜症、及び緑内障などの神経変性疾患；インスリン非依存性糖尿病（2型糖尿病など）、肥満症、躁鬱病、精神分裂病、脱毛症、及び、乳癌、非小細胞肺癌、甲状腺癌、T又はB細胞白血病、ウイルス誘導性腫瘍などの癌の治療剤となる可能性がある。

【0009】

後に記載する式（I）で表される本発明の化合物と構造的に類似する化合物として、以下の式（A）：

【化4】



（式中、Rは2，6-ジクロロベンジル基、2-（2-クロロフェニル）エチルアミノ基、3-フェニルプロピルアミノ基、又は1-メチル-3-フェニルプロピルアミノ基を表す（国際公開WO98/24782号公報））で表される化合物が知られている。式（A）で表される化合物は、ピリミジン環の5位に4-フルオロフェニル基、4位に水酸基を有することを特徴としており、本発明の範囲に包含されない。さらに、式（A）で表される化合物の主たる薬理活性は抗炎症作用であるが、式（I）で表される本発明の化合物はTPK1阻害剤又は神経変性疾患の治療薬として有用であり、従って、それらの薬理活性は互いに全く異なっている。

【特許文献1】 国際公開WO00/18758号公報

【特許文献2】 国際公開WO01/70728号公報

【特許文献3】 国際公開WO01/70729号公報

【0010】

【発明が解決しようとする課題】

本発明の課題は、アルツハイマー病などの疾患の予防及び／又は治療のための医薬の有効成分として有用な化合物を提供することにある。より詳細には、本発明の課題は、TPK1活性を阻害することによりA β の神経毒性及びPHFの形成を抑え、また神経細胞死を阻止することにより、アルツハイマー病などの神経変性疾患に対して根本的な予防及び／又は治療を可能にする医薬の有効成分として有用な新規化合物を提供することにある。

【0011】

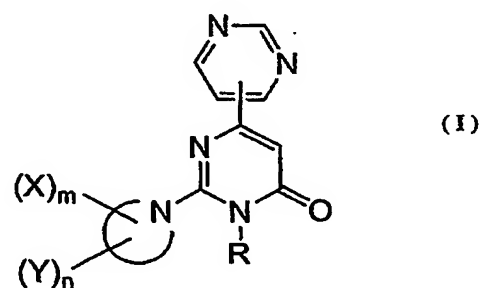
【課題を解決するための手段】

本発明者らは上記課題を解決すべく、TPK1のリン酸化能に対する阻害作用を有する各種化合物をスクリーニングした。その結果、下記式(I)で表される化合物が所望の作用を有しており、上記の疾患の予防及び／又は治療のための医薬の有効成分として有用であることを見出した。本発明はこれらの知見を基にして完成されたものである。

【0012】

すなわち本発明は、下記式(I)：

【化5】



〔式中、Rは、置換されていてもよいC₁～C₁₂のアルキル基を示し；

【0013】

【化6】



はピペラジン環またはピペリジン環を示し；

Xはそれぞれ独立して、置換されていてもよい $C_1 \sim C_8$ のアルキル基、一部が水素化されていてもよい置換されていてもよい $C_6 \sim C_{10}$ のアリール環、置換されていてもよいインダン環、酸素原子、硫黄原子、及び窒素原子から成る群から選ばれる1～4個のヘテロ原子を有し、かつ全部で5～10個の環構成原子を有する、置換されていることもあるヘテロ環、又は X^1-CO- (X^1 は置換されていてもよい $C_6 \sim C_{10}$ のアリール環、又は置換されていてもよい $C_1 \sim C_8$ のアルキル基を示す。)を示し;

mは1ないし3のいずれかの整数を示し;

Yはそれぞれ独立して、ハロゲン原子、水酸基、シアノ基、置換されていてもよい $C_1 \sim C_6$ のアルキル基、 Y^1-CO- (Y^1 は置換されていてもよい $C_6 \sim C_{10}$ のアリール環、又は置換されていてもよい $C_1 \sim C_8$ のアルキル基を示す。)、又は $Y^2-O-CO-$ (Y^2 は置換されていてもよい $C_1 \sim C_8$ のアルキル基を示す。)を示し;

nは0ないし8のいずれかの整数を示し;

XとY、又は二つのY基が同じ炭素に結合している場合には、それらはそれぞれ結合して $C_2 \sim C_6$ のアルキレン基を形成してもよく;

および、mが1のとき、nは0で、Xは X^1-CO- であり、そのとき;

(1) Xは無置換の1-ピペラジニル基の3位に結合していず、又は、4-アルキル-1-ピペラジニル基の3位に結合していず、又は

(2) Xは無置換の1-ピペリジニル基の3位又は4位に結合していない。}

で表されるピリミドン誘導体若しくはその塩、又はそれらの溶媒和物若しくはそれらの水和物を提供する。

【0014】

本発明の別の観点からは、式(I)で表される3-置換-4-ピリミドン誘導体及び生理学的に許容されるその塩、並びにそれらの溶媒和物及びそれらの水和物からなる群より選ばれる物質を有効成分として含む医薬が提供される。この医薬の好ましい態様としては、タウプロテインキナーゼ1の機能亢進に起因する疾患の予防及び／又は治療のための前記の医薬、及び神経変性疾患の予防及び／又は治療のための前記の医薬が提供される。

【0015】

本発明のさらに好ましい態様としては、該疾患が、アルツハイマー病、虚血性脳血管障害、ダウン症候群、脳アミロイドアンギオパチーによる脳出血、進行性核上麻痺、亜急性硬化性全脳炎性パーキンソン症候群、脳炎後パーキンソン症候群、拳闘家脳症、グアム・パーキンソン痴呆複合症、レビー小体病、ピック病、皮質底部変性症、前頭側頭性痴呆、血管性痴呆、急性発作及び外傷性損傷、脳及び脊髄損傷、末梢性ニューロパシー、網膜症、緑内障、インスリン非依存性糖尿病（2型糖尿病など）、肥満症、躁鬱病、精神分裂病、脱毛症、及び、乳癌、非小細胞肺癌、甲状腺癌、T又はB細胞白血病、ウイルス誘導性腫瘍などの癌から成る群から選ばれる前記の医薬；及び有効成分として上記の物質を1又は2以上の製剤用添加物と共に含む医薬組成物の形態の前記の医薬が提供される。

本発明は、さらに、式（I）の3-置換-4-ピリミドン誘導体及びその塩、並びにそれらの溶媒和物及びそれらの水和物からなる群より選ばれる物質を有効成分として含むタウプロテインキナーゼ1の阻害剤を提供する。

【0016】

本発明のさらに別の観点からは、タウプロテインキナーゼ1の機能亢進に起因する疾患の予防及び／又は治療方法であって、式（I）の3-置換-4-ピリミドン誘導体及び生理学的に許容されるその塩、並びにそれらの溶媒和物及びそれらの水和物からなる群より選ばれる物質の予防及び／又は治療有効量を患者に投与する工程を含む方法；及び、上記医薬の製造のための式（I）の3-置換-4-ピリミドン誘導体及び生理学的に許容されるその塩、並びにそれらの溶媒和物及びそれらの水和物からなる群から選ばれる物質の使用が提供される。

【0017】

【発明の実施の形態】

本発明に用いられるアルキル基は直鎖状又は分枝鎖状のいずれでもよい。

Rで表されるC₁～C₁₂のアルキル基としては、例えば、メチル基、エチル基、n-プロピル基、イソプロピル基、n-ブチル基、イソブチル基、sec-ブチル基、tert-ブチル基、n-ペンチル基、イソペンチル基、ネオペンチル基、1,1-ジメチルプロピル基、n-ヘキシル基、イソヘキシル基、直鎖状

又は分枝鎖状のヘプチル基、オクチル基、ノニル基、デシル基、ウンデシル基、又はドデシル基を挙げることができる。特に好ましいRはメチル基である。

本明細書において、機能性基が、「置換されてもよい」又は「置換されることもある」と定義している場合、置換基の数、ならびにその種類、置換位は限定されず、2又は3以上の置換基が存在する場合、それらは同じであっても異なってもよい。

【0018】

Rで示されるC₁～C₁₂のアルキル基が、1又は2以上の置換基を有する場合、該アルキル基は、例えば、シクロプロピル基、シクロブチル基、シクロペンチル基、シクロヘキシル基、シクロヘプチル基、シクロオクチル基などのC₃～C₈シクロアルキル基；メトキシ基、エトキシ基、プロポキシ基、イソプロポキシ基、ブトキシ基、イソブトキシ基、tert-ブトキシ基などのC₁～C₅アルコキシ基；C₁～C₃のアルキルアミノ基又はC₂～C₆のジアルキルアミノ基；フェニル基、1-ナフチル基、及び2-ナフチル基などのC₆～C₁₀のアリール基から成る群から選ばれる1又は2以上の置換基を有していてもよい。

【0019】

Xで示されるC₁～C₈のアルキル基は、例えば、メチル基、エチル基、n-プロピル基、イソプロピル基、n-ブチル基、イソブチル基、sec-ブチル基、tert-ブチル基、n-ペンチル基、イソペンチル基、ネオペンチル基、1,1-ジメチルプロピル基、n-ヘキシル基、イソヘキシル基、又は直鎖状若しくは分枝鎖状のヘプチル基又はオクチル基であればよい。

【0020】

Xで示される一部が水素化されていてもよいC₆～C₁₀のアリール環は、例えば、ベンゼン環、ナフタレン環、インダン環、又は1,2,3,4-テトラヒドロナフタレン環であればよい。

【0021】

Xで示される、酸素原子、硫黄原子、及び窒素原子から成る群から選ばれる1～4個のヘテロ原子を有し、かつ全部で5～10個の環構成原子を有するヘテロ環は、例えばフラン環、ジヒドロフラン環、テトラヒドロフラン環、ピラン環、

ジヒドロピラン環、テトラヒドロピラン環、ベンゾフラン環、ジヒドロベンゾフラン環、イソベンゾフラン環、ベンゾジオキソール環、クロメン環、クロマン環、イソクロマン環、チオフエン環、ベンゾチオフエン環、ピロール環、ピロリン環、ピロリジン環、イミダゾール環、イミダゾリン環、イミダゾリジン環、ピラゾール環、ピラゾリン環、ピラゾリジン環、トリアゾール環、テトラゾール環、ピリジン環、ピリジンオキシド環、ピペリジン環、ピラジン環、ピペラジン環、ピリミジン環、ピリダジン環、インドール環、インドリン環、イソインドール環、イソインドリン環、インダゾール環、ベンゾイミダゾール環、ベンゾトリアゾール環、テトラヒドロイソキノリン環、ベンゾチアゾリノン環、ベンゾキサゾリノン環、プリン環、キノリジン環、キノリン環、フタラジン環、ナフチリジン環、キノキサリン環、キナゾリン環、シンノリン環、プテリジン環、オキサゾール環、オキサゾリジン環、イソキサゾール環、イソキサゾリジン環、オキサジアゾール環、チアゾール環、ベンゾチアゾール環、チアジリジン環、イソチアゾール環、イソチアゾリジン環、ベンゾジオキソール環、ジオキサン環、ベンゾジオキサン環、ジチアン環、モルホリン環、チオモルホリン環及びフタルイミド環などが挙げられる。

【0022】

X¹又はY¹で示されるC₆～C₁₀のアリール環は、例えば、ベンゼン環、またはナフタレン環であればよい。

【0023】

X又はX¹で示される環が、1又は2以上の置換基を有している場合は、該環は、メチル基、エチル基、プロピル基、イソプロピル基、ブチル基、イソブチル基、sec-ブチル基、tert-ブチル基、ペンチル基、イソペンチル基、ネオペンチル基、1,1-ジメチルプロピル基などのC₁～C₅のアルキル基；シクロプロピル基、シクロブチル基、シクロペンチル基、シクロヘキシル基などのC₃～C₆のシクロアルキル基；シクロプロピロキシ基、シクロブチロキシ基、シクロペンチロキシ基、シクロヘキシロキシ基などのC₃～C₆のシクロアルキロキシ基；メトキシ基、エトキシ基、プロポキシ基、イソプロポキシ基、ブトキシ基、イソブトキシ基、tert-ブトキシ基、ペンチロキシ基、イソペンチロ

キシ基などのC₁～C₅のアルコキシ基；シクロプロピルメトキシ基、シクロペンチルメトキシ基などのC₄～C₇のシクロアルキルアルコキシ基；メチルチオ基、エチルチオ基、プロピルチオ基、ブチルチオ基、及びペンチルチオ基などのC₁～C₅のアルキルチオ基；メタンスルホニル基、エタンスルホニル基、プロパンスルホニル基、ブタンスルホニル基、及びペンタンスルホニル基などのC₁～C₅のアルキルスルホニル基；フッ素原子、塩素原子、臭素原子、及びヨウ素原子などのハロゲン原子；トリフルオロメチル基などのC₁～C₅のハロゲン化アルキル基；水酸基；シアノ基；ニトロ基；ホルミル基；アセチル基、プロピオニル基、ブチリル基、及びバレリル基などのC₂～C₆のアルキルカルボニル基；置換されていてもよいベンゼン環、置換されていてもよいナフタレン環、酸素原子、硫黄原子、及び窒素原子から成る群から選ばれる1～4個のヘテロ原子を有し、かつ全部で5～10個の環構成原子を有する、置換されていることもあるヘテロ環、置換されていてもよいフェノキシ基；置換されていてもよいフェニルアミノ基；アミノ基；メチルアミノ基、エチルアミノ基、プロピルアミノ基、イソプロピルアミノ基、ブチルアミノ基、イソブチルアミノ基、tert-ブチルアミノ基、ペンチルアミノ基、及びイソペンチルアミノ基などのC₁～C₅のモノアルキルアミノ基；ジメチルアミノ基、エチルメチルアミノ基、ジエチルアミノ基、メチルプロピルアミノ基、及びジイソプロピルアミノ基などのC₂～C₁₀のジアルキルアミノ基；メチルアミノメチル基、エチルアミノメチル基、プロピルアミノメチル基、イソプロピルアミノメチル基、ブチルアミノメチル基、イソブチルアミノメチル基、tert-ブチルアミノメチル基、ペンチルアミノメチル基、イソペンチルアミノメチル基などのC₁～C₅のモノアルキルアミノメチル基；ジメチルアミノメチル基、ジエチルアミノメチル基、エチルメチルアミノメチル基、メチルプロピルアミノメチル基などのC₂～C₁₀のジアルキルアミノメチル基；ピロリジニルメチル基；ピペリジニルメチル基；モルホリノメチル基；ピペラジニルメチル基；ピロリルメチル基；イミダゾリルメチル基；ピラゾリルメチル基；及びトリアゾリルメチル基から成る群から選ばれる1又は2以上の置換基を有していてもよい。

【0024】

Y¹で示されるC₆～C₁₀のアリール環が、1又は2以上の置換基を有している場合は、該環は、ハロゲン原子、C₁～C₅アルキル基、C₃～C₆シクロアルキル基、C₃～C₆シクロアルキロキシ基、C₁～C₅アルコキシ基、C₄～C₇シクロアルキルアルコキシ基、C₁～C₅アルキルチオ基、C₁～C₅アルキルスルホニル基、C₁～C₅ハロゲン化アルキル基、及びベンゼン環から成る群から選ばれる1又は2以上の置換基を有していてもよい。

【0025】

X、X¹又はY¹で示される環が、1又は2以上の置換基を有している場合は、該置換基はさらに、メチル基、エチル基、プロピル基、イソプロピル基、ブチル基、イソブチル基、sec-ブチル基、tert-ブチル基、ペンチル基、イソペンチル基、ネオペンチル基、1, 1-ジメチルプロピル基などのC₁～C₅のアルキル基；シクロプロピル基、シクロブチル基、シクロペンチル基、シクロヘキシル基などのC₃～C₆のシクロアルキル基；シクロプロピロキシ基、シクロブチロキシ基、シクロペンチロキシ基、シクロヘキシロキシ基などのC₃～C₆のシクロアルキロキシ基；水酸基；メトキシ基、エトキシ基、プロポキシ基、イソプロポキシ基、ブトキシ基、イソブトキシ基、tert-ブトキシ基、ペンチロキシ基、イソペンチロキシ基などのC₁～C₅のアルコキシ基；シクロプロピルメトキシ基、シクロペンチルメトキシ基などのC₄～C₇のシクロアルキルアルコキシ基；メチルチオ基、エチルチオ基、プロピルチオ基、ブチルチオ基、及びペンチルチオ基などのC₁～C₅のアルキルチオ基；メタンスルホニル基、エタンスルホニル基、プロパンスルホニル基、ブタンスルホニル基、及びペンタンスルホニル基などのC₁～C₅のアルキルスルホニル基；フッ素原子、塩素原子、臭素原子、及びヨウ素原子などのハロゲン原子；トリフルオロメチル基などのC₁～C₅のハロゲン化アルキル基；トリフルオロメトキシ基、2, 2, 2-トリフルオロエトキシ基などのC₁～C₅のハロゲン化アルコキシ基；水酸基；シアノ基；ニトロ基；ホルミル基；アセチル基、プロピオニル基、ブチリル基、及びバレリル基などのC₂～C₆のアルキルカルボニル基；アミノ基；メチルアミノ基、エチルアミノ基、プロピルアミノ基、イソプロピルアミノ基、ブチルアミノ基、イソブチルアミノ基、tert-ブチルアミノ基、ペンチルアミノ基、

及びイソペンチルアミノ基などのC₁～C₅のモノアルキルアミノ基；ジメチルアミノ基、エチルメチルアミノ基、ジエチルアミノ基、メチルプロピルアミノ基、及びジイソプロピルアミノ基などのC₂～C₁₀のジアルキルアミノ基；メチルアミノメチル基、エチルアミノメチル基、プロピルアミノメチル基、イソプロピルアミノメチル基、ブチルアミノメチル基、イソブチルアミノメチル基、tert-ブチルアミノメチル基、ペンチルアミノメチル基、イソペンチルアミノメチル基などのC₂～C₁₀のモノアルキルアミノメチル基；ジメチルアミノメチル基、ジエチルアミノメチル基、エチルメチルアミノメチル基、メチルプロピルアミノメチル基などのC₃～C₁₁のジアルキルアミノメチル基などから成る群から選ばれる1又は2以上の置換基を有していてもよい。

【0026】

Rは好ましくはC₁～C₃アルキル基、より好ましくはメチル基又はエチル基である。アルキル基の置換基は好ましくはC₃～C₈アルキル基である。

【0027】

Xは、好ましくは置換されていてもよいベンゼン環、置換されていてもよいベンジル基、置換されていてもよいナフチル基、置換されていてもよいベンゾフラン環、置換されていてもよいジヒドロベンゾフラン環、置換されていてもよいベンゾチオフェン環、置換されていてもよいベンゾキサゾール環、置換されていてもよいベンゾイソキサゾール環、より好ましくは置換されていてもよいベンゼン環、置換されていてもよいベンジル基である。Xの置換基は、好ましくは、ハロゲン原子、C₁～C₄アルキル基、C₁～C₄アルコキシ基、水酸基、ニトロ基、シアノ基、過ハロゲン化C₁～C₄アルキル基、カルボキシル基、C₁～C₄アルコキシカルボニル基、C₁～C₄アルキルチオ基、C₁～C₄アルコキシスルホニル基、C₁～C₄アルキル基で置換されていてもよいアミノ基からなる群から選ばれる。

【0028】

前記の式(I)で表される化合物は塩を形成する場合がある。塩の例としては、酸性基が存在する場合には、リチウム、ナトリウム、カリウム、マグネシウム、カルシウム等のアルカリ金属及びアルカリ土類金属塩；アンモニア、及びメチ

ルアミン、ジメチルアミン、トリメチルアミン、ジシクロヘキシルアミン、トリス（ヒドロキシメチル）アミノメタン、N, N-ビス（ヒドロキシエチル）ピペラジン、2-アミノ-2-メチル-1-プロパノール、エタノールアミン、N-メチルグルカミン、L-グルカミン等のアミンの塩；又はリジン、 δ -ヒドロキシリジン、及びアルギニンなどの塩基性アミノ酸との塩が挙げられる。塩基性基が存在する場合には、例として、塩酸、臭化水素酸、硫酸、硝酸、リン酸等の鉱酸との塩；メタンスルホン酸、ベンゼンスルホン酸、パラトルエンスルホン酸、酢酸、プロピオン酸、酒石酸、フマル酸、マレイン酸、リンゴ酸、シュウ酸、コハク酸、クエン酸、安息香酸、マンデル酸、ケイ皮酸、乳酸、グリコール酸、グルクロン酸、アスコルビン酸、ニコチン酸、サリチル酸等の有機酸との塩；又はアスパラギン酸、グルタミン酸などの酸性アミノ酸との塩が挙げられる。

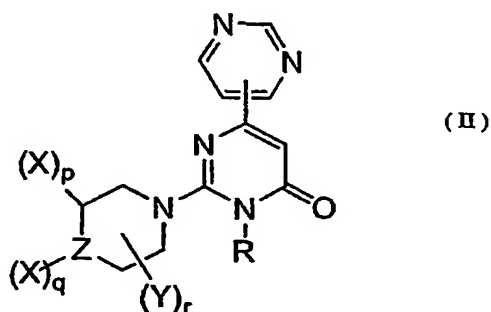
【0029】

本発明の範囲には、前記式（I）で表される3-置換-4-ピリミドン誘導体及びその塩に加えて、それらの溶媒和物及び水和物も包含される。また、前記式（I）で表される3-置換-4-ピリミドン誘導体は1個又は2個以上の不斉炭素を有する場合があるが、不斉炭素の立体化学についてはそれぞれ独立して（R）体又は（S）体のいずれかをとることができ、該ピリミドン誘導体は光学異性体又はジアステレオ異性体などの立体異性体として存在することがある。純粋な形態の任意の立体異性体、立体異性体の任意の混合物、ラセミ体などは、いずれも本発明の範囲に包含される。

【0030】

本発明の好適な化合物は式（II）：

【化7】



{式中、R、X、Yは上記と同義であり；

pは0又は1であり；qは0または1であり；rは0ないし6のいずれかの整数であり；p+qは1または2であり；ZはNまたはCZ¹（Z¹は水素原子またはYを示す。）を示す。} で表される。

【0031】

式（II）で表される化合物のより好適な種類の例としては：

（1）RがC₃～C₈のシクロアルキル基で置換されていてもよいC₁～C₃のアルキル基であるもの；

（2）Rがメチル基またはエチル基であり、Yがピペラジン環又はピペリジン環の3位、4位又は5位にあり、p+qが1であり、およびrが0ないし3のいずれかの整数である上記（1）の化合物；

（3）Xが置換されていてもよいC₁～C₈のアルキル基、又は置換されていてもよいC₆～C₁₀のアリール環であり、Yが置換されていてもよいC₁～C₆のアルキル基であり、pが1であり、qが0であり、rが0ないし3のいずれかの整数であり、ZがN又はCHである上記（2）の化合物；

（4）Xが置換されていてもよいベンゼン環、置換されていてもよいベンジル基であり、Yが置換されていてもよいメチル基であり、ZがNであり、およびrが0又は1である上記（3）の化合物；

（5）Xが置換されていてもよいベンゼン環、置換されていてもよいベンジル基、置換されていてもよいベンゾイル基、置換されていてもよいベンゾイソチアゾール環であり、Yが置換されていてもよいメチル基であり、ZがNであり、およびpが0である上記（2）の化合物。

（6）Xが置換されていてもよいベンゼン環で置換されたC₁～C₈のアルキル基、又は置換されていてもよいベンゼン環であり、Yが水酸基、シアノ基、又はY¹-CO-（Y¹はC₁～C₈のアルキル基である。）であり、ZがCHまたはC-Yであり、及びrが0又は1である上記（2）の化合物；

（7）Xが置換されていてもよいベンジル基、又は置換されていてもよいベンゼン環であり、又は置換されていてもよいベンゼン環であり、Yが水酸基、シアノ基、又はアセチル基であり、ZがCHまたはC-Yであり、及びrが0又は1で

ある上記(6)の化合物。

が挙げられる。

【0032】

式(II)で表される化合物の特に好適な種類の例としては:

- (1) Rがメチル基であり、Yが $\text{CH}_3\text{O}-\text{CO}-$ 基又は $\text{CH}_3\text{CH}_2\text{O}-\text{CO}-$ 基であり、ZがNであり、pが0であり、qが1であり、rが0又は1であり、及びYがピペラジン環の3位にあるもの;
- (2) Rがメチル基であり、Yがメチル基、ベンジル基、またはアセチル基であり、ZがNであり、pが1であり、qが0であり、rが0又は1であり、及びYがピペラジン環の4位にあるもの;
- (3) Rがメチル基であり、Yがメチル基であり、ZがNであり、pが1であり、qが0であり、rが1ないし3であり、及びYがピペラジン環の3位、4位又は5位にあるもの;
- (4) Rがメチル基であり、Yが水酸基、又はシアノ基であり、ZがCHであり、pが1であり、qが0であり、rが0又は1であり、及びXとYが同じ炭素に結合しているもの;
- (5) Rがメチル基であり、Yが水酸基、又はシアノ基、またはアセチル基であり、ZがC-Yであり、pが0であり、qが1であり、rが1であるもの。

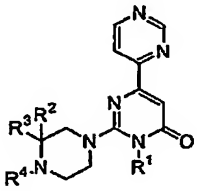







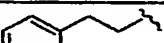
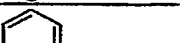


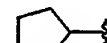

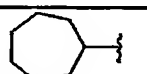





が挙げられる。

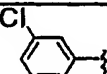
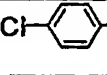
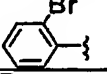
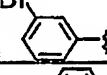
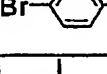
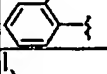
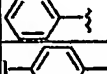
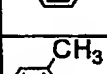
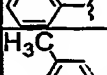
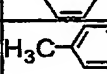
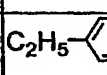
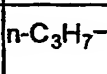
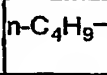
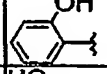
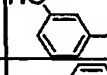
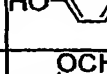
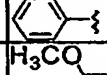
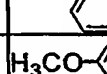
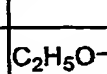


本発明の好適な化合物の例を以下の表に示すが、本発明の範囲は次の化合物に限定されない。

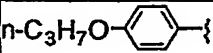
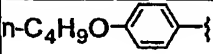

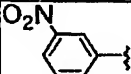


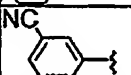
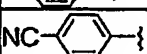

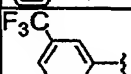
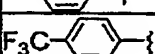

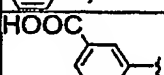
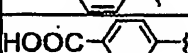
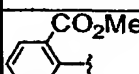
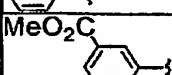
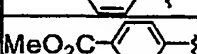
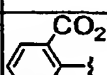
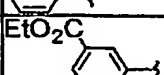
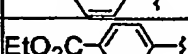
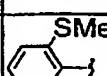
【0033】

【表 1】

Table-1

				
No.	R1	R2	R3	R4
A0001	CH3-	H	H	CH3-
A0002	CH3-	H	H	CH3CH2-
A0003	CH3-	H	H	
A0004	CH3-	H	H	
A0005	CH3-	H	H	
A0006	CH3-	H	H	
A0007	CH3-	H	H	
A0008	CH3-	H	H	
A0009	CH3-	H	H	
A0010	CH3-	H	H	
A0011	CH3-	H	H	
A0012	CH3-	H	H	
A0013	CH3-	H	H	
A0014	CH3-	H	H	
A0015	CH3-	H	H	
A0016	CH3-	H	H	
A0017	CH3-	H	H	
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A0020	CH3-	H	H	
A0021	CH3-	H	H	

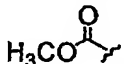

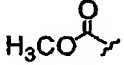
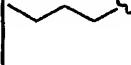
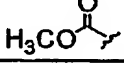
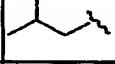
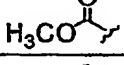
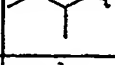
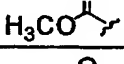

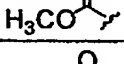
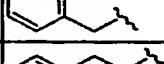
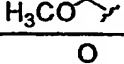
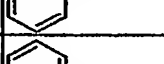
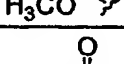

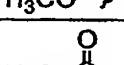

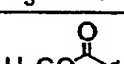

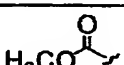

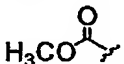
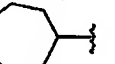
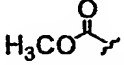
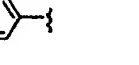
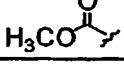

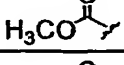

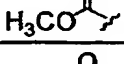

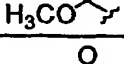
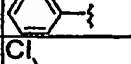
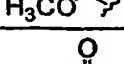

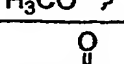

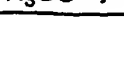
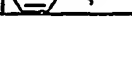


No.	R1	R2	R3	R4
A0022	CH ₃ -	H	H	
A0023	CH ₃ -	H	H	
A0024	CH ₃ -	H	H	
A0025	CH ₃ -	H	H	
A0026	CH ₃ -	H	H	
A0027	CH ₃ -	H	H	
A0028	CH ₃ -	H	H	
A0029	CH ₃ -	H	H	
A0030	CH ₃ -	H	H	
A0031	CH ₃ -	H	H	
A0032	CH ₃ -	H	H	
A0033	CH ₃ -	H	H	
A0034	CH ₃ -	H	H	
A0035	CH ₃ -	H	H	
A0036	CH ₃ -	H	H	
A0037	CH ₃ -	H	H	
A0038	CH ₃ -	H	H	
A0039	CH ₃ -	H	H	
A0040	CH ₃ -	H	H	
A0041	CH ₃ -	H	H	
A0042	CH ₃ -	H	H	

No.	R1	R2	R3	R4
A0043	CH ₃ -	H	H	
A0044	CH ₃ -	H	H	
A0045	CH ₃ -	H	H	
A0046	CH ₃ -	H	H	
A0047	CH ₃ -	H	H	
A0048	CH ₃ -	H	H	
A0049	CH ₃ -	H	H	
A0050	CH ₃ -	H	H	
A0051	CH ₃ -	H	H	
A0052	CH ₃ -	H	H	
A0053	CH ₃ -	H	H	
A0054	CH ₃ -	H	H	
A0055	CH ₃ -	H	H	
A0056	CH ₃ -	H	H	
A0057	CH ₃ -	H	H	
A0058	CH ₃ -	H	H	
A0059	CH ₃ -	H	H	
A0060	CH ₃ -	H	H	
A0061	CH ₃ -	H	H	
A0062	CH ₃ -	H	H	
A0063	CH ₃ -	H	H	

No.	R1	R2	R3	R4
A0064	CH ₃ -	H	H	
A0065	CH ₃ -	H	H	
A0066	CH ₃ -	H	H	
A0067	CH ₃ -	H	H	
A0068	CH ₃ -	H	H	
A0069	CH ₃ -	H	H	
A0070	CH ₃ -	H	H	
A0071	CH ₃ -	H	H	
A0072	CH ₃ -	H	H	
A0073	CH ₃ -	H	H	
A0074	CH ₃ -	H	H	
A0075	CH ₃ -	H	H	
A0076	CH ₃ -	H	H	
A0077	CH ₃ -	H	H	
A0078	CH ₃ -	H	H	
A0079	CH ₃ -	H	H	
A0080	CH ₃ -	H	H	
A0081	CH ₃ -	H	H	
A0082	CH ₃ -	H	H	
A0083	CH ₃ -	H	H	
A0084	CH ₃ -	H	H	

No.	R1	R2	R3	R4
A0085	CH ₃ -	H	H	
A0086	CH ₃ -	H	H	
A0087	CH ₃ -	H	H	
A0088	CH ₃ -	H	H	
A0089	CH ₃ -	H	H	
A0090	CH ₃ -	H	H	
A0091	CH ₃ -	H	H	
A0092	CH ₃ -	H	H	
A0093	CH ₃ -	H	H	
A0094	CH ₃ -	H	H	
A0095	CH ₃ -	H	H	
A0096	CH ₃ -	H	H	
A0097	CH ₃ -	H	H	
A0098	CH ₃ -	H	H	
A0099	CH ₃ -	H	H	
A0100	CH ₃ -	H	H	
A0101	CH ₃ -	H	H	
A0102	CH ₃ -	H	H	
A0103	CH ₃ -	H	H	
A0104	CH ₃ -	H	H	
A0105	CH ₃ -	H	H	

No.	R1	R2	R3	R4
A0106	CH ₃ -	H	H	
A0107	CH ₃ -	H	H	
A0108	CH ₃ -	H	H	
A0109	CH ₃ -	H	H	
A0110	CH ₃ -	H	H	
A0111	CH ₃ -	H	H	
A0112	CH ₃ -	H	H	
A0113	CH ₃ -	H	H	
A0114	CH ₃ -	H	H	
A0115	CH ₃ -	H	H	
A0116	CH ₃ -	H	H	
A0117	CH ₃ -	H	H	
A0118	CH ₃ -	H	H	
A0119	CH ₃ -	H	H	
A0120	CH ₃ -	H	H	
A0121	CH ₃ -	H	H	
A0122	CH ₃ -	H	H	
A0123	CH ₃ -		H	H
A0124	CH ₃ -		H	CH ₃ -
A0125	CH ₃ -		H	CH ₃ CH ₂ -
A0126	CH ₃ -		H	

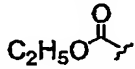




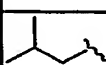


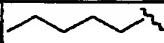
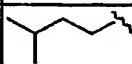
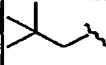


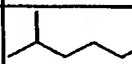



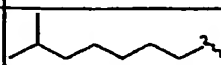
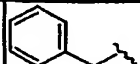
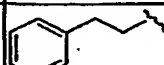
No.	R1	R2	R3	R4
A0127	CH ₃ -		H	
A0128	CH ₃ -		H	
A0129	CH ₃ -		H	
A0130	CH ₃ -		H	
A0131	CH ₃ -		H	
A0132	CH ₃ -		H	
A0133	CH ₃ -		H	
A0134	CH ₃ -		H	
A0135	CH ₃ -		H	
A0136	CH ₃ -		H	
A0137	CH ₃ -		H	
A0138	CH ₃ -		H	
A0139	CH ₃ -		H	
A0140	CH ₃ -		H	
A0141	CH ₃ -		H	
A0142	CH ₃ -		H	
A0143	CH ₃ -		H	
A0144	CH ₃ -		H	
A0145	CH ₃ -		H	
A0146	CH ₃ -		H	
A0147	CH ₃ -		H	

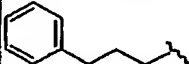




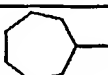















No.	R1	R2	R3	R4
A0148	CH ₃ -		H	
A0149	CH ₃ -		H	
A0150	CH ₃ -		H	
A0151	CH ₃ -		H	
A0152	CH ₃ -		H	
A0153	CH ₃ -		H	
A0154	CH ₃ -		H	
A0155	CH ₃ -		H	
A0156	CH ₃ -		H	
A0157	CH ₃ -		H	
A0158	CH ₃ -		H	
A0159	CH ₃ -		H	
A0160	CH ₃ -		H	
A0161	CH ₃ -		H	
A0162	CH ₃ -		H	
A0163	CH ₃ -		H	
A0164	CH ₃ -		H	
A0165	CH ₃ -		H	
A0166	CH ₃ -		H	
A0167	CH ₃ -		H	
A0168	CH ₃ -		H	

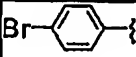
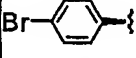
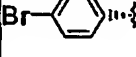


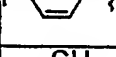

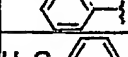
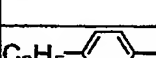
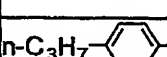
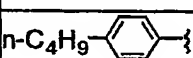
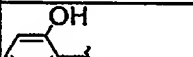

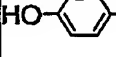
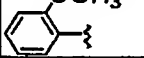
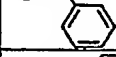

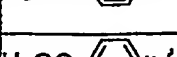
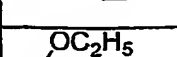
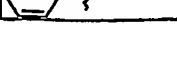

No.	R1	R2	R3	R4
A0169	CH ₃ -		H	
A0170	CH ₃ -		H	
A0171	CH ₃ -		H	
A0172	CH ₃ -		H	
A0173	CH ₃ -		H	
A0174	CH ₃ -		H	
A0175	CH ₃ -		H	
A0176	CH ₃ -		H	
A0177	CH ₃ -		H	
A0178	CH ₃ -		H	H
A0179	CH ₃ -		H	CH ₃ -
A0180	CH ₃ -		H	CH ₃ CH ₂ -
A0181	CH ₃ -		H	
A0182	CH ₃ -		H	
A0183	CH ₃ -		H	
A0184	CH ₃ -		H	
A0185	CH ₃ -		H	
A0186	CH ₃ -		H	
A0187	CH ₃ -		H	
A0188	CH ₃ -		H	
A0189	CH ₃ -		H	

No.	R1	R2	R3	R4
A0190	CH3-		H	
A0191	CH3-		H	
A0192	CH3-		H	
A0193	CH3-		H	
A0194	CH3-		H	
A0195	CH3-		H	
A0196	CH3-		H	
A0197	CH3-		H	
A0198	CH3-		H	
A0199	CH3-		H	
A0200	CH3-		H	
A0201	CH3-		H	
A0202	CH3-		H	
A0203	CH3-		H	
A0204	CH3-		H	
A0205	CH3-		H	
A0206	CH3-		H	
A0207	CH3-		H	
A0208	CH3-		H	
A0209	CH3-		H	
A0210	CH3-		H	

No.	R1	R2	R3	R4
A0211	CH3-		H	
A0212	CH3-		H	
A0213	CH3-		H	
A0214	CH3-		H	
A0215	CH3-		H	
A0216	CH3-		H	
A0217	CH3-		H	
A0218	CH3-		H	
A0219	CH3-		H	
A0220	CH3-		H	
A0221	CH3-		H	
A0222	CH3-		H	
A0223	CH3-		H	
A0224	CH3-		H	
A0225	CH3-		H	
A0226	CH3-		H	
A0227	CH3-		H	
A0228	CH3-		H	
A0229	CH3-		H	
A0230	CH3-		H	
A0231	CH3-		H	

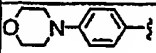
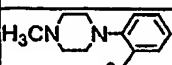

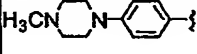
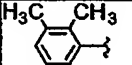
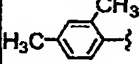


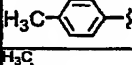


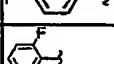


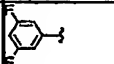


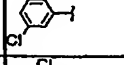



No.	R1	R2	R3	R4
A0232	CH3-		H	
A0233	CH3-	CH3-	H	H
A0234	CH3-	CH3CH2-	H	H
A0235	CH3-		H	H
A0236	CH3-		H	H
A0237	CH3-		H	H
A0238	CH3-		H	H
A0239	CH3-		H	H
A0240	CH3-		H	H
A0241	CH3-		H	H
A0242	CH3-		H	H
A0243	CH3-		H	H
A0244	CH3-		H	H
A0245	CH3-		H	H
A0246	CH3-		H	H
A0247	CH3-		H	H
A0248	CH3-		H	H
A0249	CH3-		H	H
A0250	CH3-		H	H
A0251	CH3-		H	H
A0252	CH3-		H	H


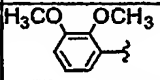
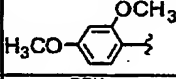
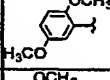

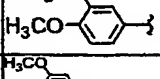
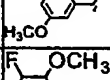
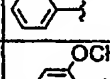
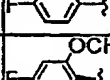
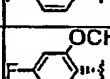
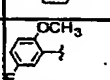
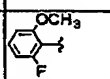
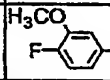
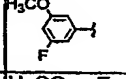
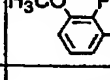
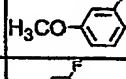
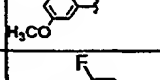
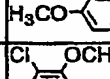
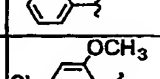
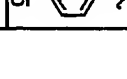

No.	R1	R2	R3	R4
A0253	CH3-		H	H
A0254	CH3-		H	H
A0255	CH3-		H	H
A0256	CH3-		H	H
A0257	CH3-		H	H
A0258	CH3-		H	H
A0259	CH3-		H	H
A0260	CH3-		H	H
A0261	CH3-		H	H
A0262	CH3-		H	H
A0263	CH3-		H	H
A0264	CH3-		H	H
A0265	CH3-		H	H
A0266	CH3-		H	H
A0267	CH3-		H	H
A0268	CH3-		H	H
A0269	CH3-		H	H
A0270	CH3-		H	H
A0271	CH3-		H	H
A0272	CH3-		H	H
A0273	CH3-		H	H



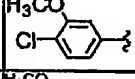

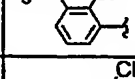
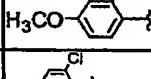

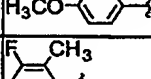

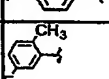


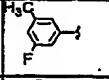

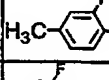
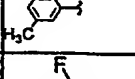

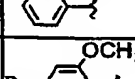
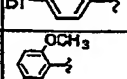
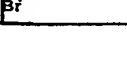

No.	R1	R2	R3	R4
A0274	CH3-		H	H
A0275	CH3-		H	H
A0276	CH3-		H	H
A0277	CH3-		H	H
A0278	CH3-		H	H
A0279	CH3-		H	H
A0280	CH3-		H	H
A0281	CH3-		H	H
A0282	CH3-		H	H
A0283	CH3-		H	H
A0284	CH3-		H	H
A0285	CH3-		H	H
A0286	CH3-		H	H
A0287	CH3-		H	H
A0288	CH3-		H	H
A0289	CH3-		H	H
A0290	CH3-		H	H
A0291	CH3-		H	H
A0292	CH3-		H	H
A0293	CH3-		H	H
A0294	CH3-		H	H


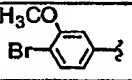

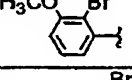
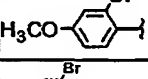

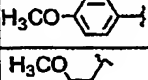
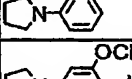
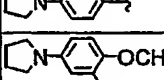
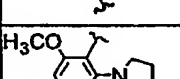
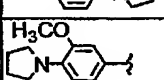
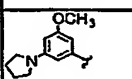



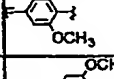
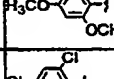
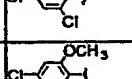

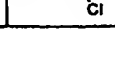

No.	R1	R2	R3	R4
A0295	CH3-		H	H
A0296	CH3-		H	H
A0297	CH3-		H	H
A0298	CH3-		H	H
A0299	CH3-		H	H
A0300	CH3-		H	H
A0301	CH3-		H	H
A0302	CH3-		H	H
A0303	CH3-		H	H
A0304	CH3-		H	H
A0305	CH3-		H	H
A0306	CH3-		H	H
A0307	CH3-		H	H
A0308	CH3-		H	H
A0309	CH3-		H	H
A0310	CH3-		H	H
A0311	CH3-		H	H
A0312	CH3-		H	H
A0313	CH3-		H	H
A0314	CH3-		H	H
A0315	CH3-		H	H

No.	R1	R2	R3	R4
A0316	CH3-		H	H
A0317	CH3-		H	H
A0318	CH3-		H	H
A0319	CH3-		H	H
A0320	CH3-		H	H
A0321	CH3-		H	H
A0322	CH3-		H	H
A0323	CH3-		H	H
A0324	CH3-		H	H
A0325	CH3-		H	H
A0326	CH3-		H	H
A0327	CH3-		H	H
A0328	CH3-		H	H
A0329	CH3-		H	H
A0330	CH3-		H	H
A0331	CH3-		H	H
A0332	CH3-		H	H
A0333	CH3-		H	H
A0334	CH3-		H	H
A0335	CH3-		H	H
A0336	CH3-		H	H

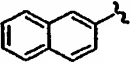




















No.	R1	R2	R3	R4
A0337	CH3-		H	H
A0338	CH3-		H	H
A0339	CH3-		H	H
A0340	CH3-		H	H
A0341	CH3-		H	H
A0342	CH3-		H	H
A0343	CH3-		H	H
A0344	CH3-		H	H
A0345	CH3-		H	H
A0346	CH3-		H	H
A0347	CH3-		H	H
A0348	CH3-		H	H
A0349	CH3-		H	H
A0350	CH3-		H	H
A0351	CH3-		H	H
A0352	CH3-		H	H
A0353	CH3-		H	H
A0354	CH3-		H	H
A0355	CH3-		H	H
A0356	CH3-		H	H
A0357	CH3-		H	H






















No.	R1	R2	R3	R4
A0358	CH3-		H	H
A0359	CH3-		H	H
A0360	CH3-		H	H
A0361	CH3-		H	H
A0362	CH3-		H	H
A0363	CH3-		H	H
A0364	CH3-		H	H
A0365	CH3-		H	H
A0366	CH3-		H	H
A0367	CH3-		H	H
A0368	CH3-		H	H
A0369	CH3-		H	H
A0370	CH3-		H	H
A0371	CH3-		H	H
A0372	CH3-		H	H
A0373	CH3-		H	H
A0374	CH3-		H	H
A0375	CH3-		H	H
A0376	CH3-		H	H
A0377	CH3-		H	H
A0378	CH3-		H	H






















No.	R1	R2	R3	R4
A0379	CH3-		H	H
A0380	CH3-		H	H
A0381	CH3-		H	H
A0382	CH3-		H	H
A0383	CH3-		H	H
A0384	CH3-		H	H
A0385	CH3-		H	H
A0386	CH3-		H	H
A0387	CH3-		H	H
A0388	CH3-		H	H
A0389	CH3-		H	H
A0390	CH3-		H	H
A0391	CH3-		H	H
A0392	CH3-		H	H
A0393	CH3-		H	H
A0394	CH3-		H	H
A0395	CH3-		H	H
A0396	CH3-		H	H
A0397	CH3-		H	H
A0398	CH3-		H	H
A0399	CH3-		H	H

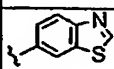
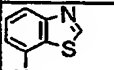
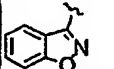
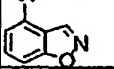
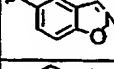
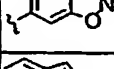
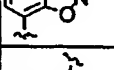
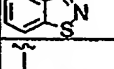
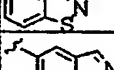
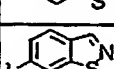
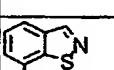
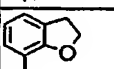
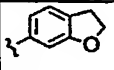
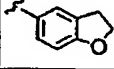
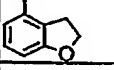
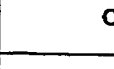

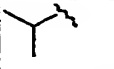
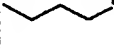
No.	R1	R2	R3	R4
A0400	CH3-		H	H
A0401	CH3-		H	H
A0402	CH3-		H	H
A0403	CH3-		H	H
A0404	CH3-		H	H
A0405	CH3-		H	H
A0406	CH3-		H	H
A0407	CH3-		H	H
A0408	CH3-		H	H
A0409	CH3-		H	H
A0410	CH3-		H	H
A0411	CH3-		H	H
A0412	CH3-		H	H
A0413	CH3-		H	H
A0414	CH3-		H	H
A0415	CH3-		H	H
A0416	CH3-		H	H
A0417	CH3-		H	H
A0418	CH3-		H	H
A0419	CH3-		H	H
A0420	CH3-		H	H






















No.	R1	R2	R3	R4
A0421	CH3-		H	H
A0422	CH3-		H	H
A0423	CH3-		H	H
A0424	CH3-		H	H
A0425	CH3-		H	H
A0426	CH3-		H	H
A0427	CH3-		H	H
A0428	CH3-		H	H
A0429	CH3-		H	H
A0430	CH3-		H	H
A0431	CH3-		H	H
A0432	CH3-		H	H
A0433	CH3-		H	H
A0434	CH3-		H	H
A0435	CH3-		H	H
A0436	CH3-		H	H
A0437	CH3-		H	H
A0438	CH3-		H	H
A0439	CH3-		H	H
A0440	CH3-		H	H
A0441	CH3-		H	H






















No.	R1	R2	R3	R4
A0442	CH3-		H	H
A0443	CH3-		H	H
A0444	CH3-		H	H
A0445	CH3-		H	H
A0446	CH3-		H	H
A0447	CH3-		H	H
A0448	CH3-		H	H
A0449	CH3-		H	H
A0450	CH3-		H	H
A0451	CH3-		H	H
A0452	CH3-		H	H
A0453	CH3-		H	H
A0454	CH3-		H	H
A0455	CH3-		H	H
A0456	CH3-		H	H
A0457	CH3-		H	H
A0458	CH3-		H	H
A0459	CH3-		H	H
A0460	CH3-		H	H
A0461	CH3-		H	H
A0462	CH3-		H	H

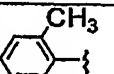
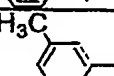
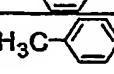
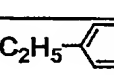
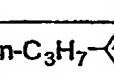
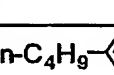
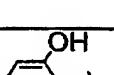
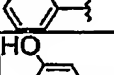
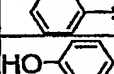
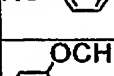
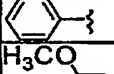
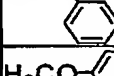
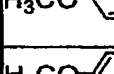
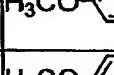
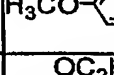
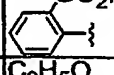
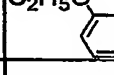
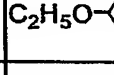
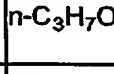
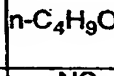
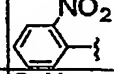
No.	R1	R2	R3	R4
A0463	CH3-		H	H
A0464	CH3-		H	H
A0465	CH3-		H	H
A0466	CH3-		H	H
A0467	CH3-		H	H
A0468	CH3-		H	H
A0469	CH3-		H	H
A0470	CH3-		H	H
A0471	CH3-		H	H
A0472	CH3-		H	H
A0473	CH3-		H	H
A0474	CH3-		H	H
A0475	CH3-		H	H
A0476	CH3-		H	H
A0477	CH3-		H	H
A0478	CH3-		H	H
A0479	CH3-		H	H
A0480	CH3-		H	H
A0481	CH3-		H	H
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A0483	CH3-		H	H

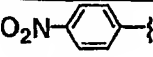


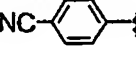

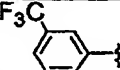
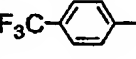
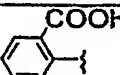
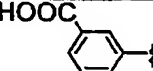
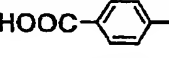
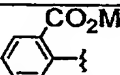
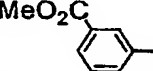
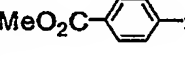
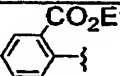
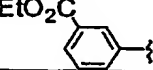
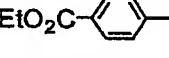


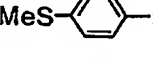
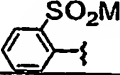
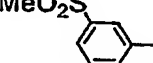
No.	R1	R2	R3	R4
A0484	CH3-		H	H
A0485	CH3-		H	H
A0486	CH3-		H	H
A0487	CH3-		H	H
A0488	CH3-		H	H
A0489	CH3-		H	H
A0490	CH3-		H	H
A0491	CH3-		H	H
A0492	CH3-		H	H
A0493	CH3-		H	H
A0494	CH3-		H	H
A0495	CH3-		H	H
A0496	CH3-		H	H
A0497	CH3-		H	H
A0498	CH3-		H	H
A0499	CH3-		H	H
A0500	CH3-		H	H
A0501	CH3-		H	H
A0502	CH3-		H	H
A0503	CH3-		H	H
A0504	CH3-		H	H

No.	R1	R2	R3	R4
A0505	CH3-		H	H
A0506	CH3-		H	H
A0507	CH3-		H	H
A0508	CH3-		H	H
A0509	CH3-		H	H
A0510	CH3-		H	H
A0511	CH3-		H	H
A0512	CH3-		H	H
A0513	CH3-		H	H
A0514	CH3-		H	H
A0515	CH3-		H	H
A0516	CH3-		H	H
A0517	CH3-		H	H
A0518	CH3-		H	H
A0519	CH3-		H	H
A0520	CH3-		H	H
A0521	CH3-	CH3-	H	CH3
A0522	CH3-	CH3CH2-	H	CH3
A0523	CH3-		H	CH3
A0524	CH3-		H	CH3
A0525	CH3-		H	CH3






















No.	R1	R2	R3	R4
A0526	CH3-		H	CH3
A0527	CH3-		H	CH3
A0528	CH3-		H	CH3
A0529	CH3-		H	CH3
A0530	CH3-		H	CH3
A0531	CH3-		H	CH3
A0532	CH3-		H	CH3
A0533	CH3-		H	CH3
A0534	CH3-		H	CH3
A0535	CH3-		H	CH3
A0536	CH3-		H	CH3
A0537	CH3-		H	CH3
A0538	CH3-		H	CH3
A0539	CH3-		H	CH3
A0540	CH3-		H	CH3
A0541	CH3-		H	CH3
A0542	CH3-		H	CH3
A0543	CH3-		H	CH3
A0544	CH3-		H	CH3
A0545	CH3-		H	CH3
A0546	CH3-		H	CH3




















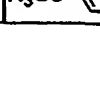

No.	R1	R2	R3	R4
A0547	CH3-		H	CH3
A0548	CH3-		H	CH3
A0549	CH3-		H	CH3
A0550	CH3-		H	CH3
A0551	CH3-		H	CH3
A0552	CH3-		H	CH3
A0553	CH3-		H	CH3
A0554	CH3-		H	CH3
A0555	CH3-		H	CH3
A0556	CH3-		H	CH3
A0557	CH3-		H	CH3
A0558	CH3-		H	CH3
A0559	CH3-		H	CH3
A0560	CH3-		H	CH3
A0561	CH3-		H	CH3
A0562	CH3-		H	CH3
A0563	CH3-		H	CH3
A0564	CH3-		H	CH3
A0565	CH3-		H	CH3
A0566	CH3-		H	CH3
A0567	CH3-		H	CH3


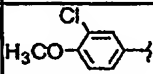

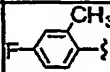


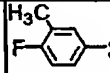

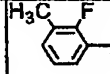
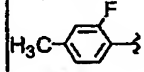

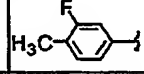
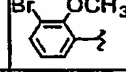
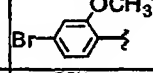


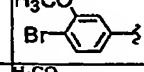
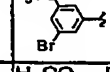
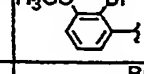
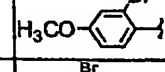
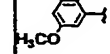
No.	R1	R2	R3	R4
A0568	CH ₃ -		H	CH ₃
A0569	CH ₃ -		H	CH ₃
A0570	CH ₃ -		H	CH ₃
A0571	CH ₃ -		H	CH ₃
A0572	CH ₃ -		H	CH ₃
A0573	CH ₃ -		H	CH ₃
A0574	CH ₃ -		H	CH ₃
A0575	CH ₃ -		H	CH ₃
A0576	CH ₃ -		H	CH ₃
A0577	CH ₃ -		H	CH ₃
A0578	CH ₃ -		H	CH ₃
A0579	CH ₃ -		H	CH ₃
A0580	CH ₃ -		H	CH ₃
A0581	CH ₃ -		H	CH ₃
A0582	CH ₃ -		H	CH ₃
A0583	CH ₃ -		H	CH ₃
A0584	CH ₃ -		H	CH ₃
A0585	CH ₃ -		H	CH ₃
A0586	CH ₃ -		H	CH ₃
A0587	CH ₃ -		H	CH ₃
A0588	CH ₃ -		H	CH ₃

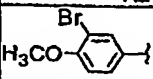
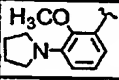
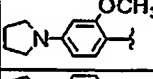
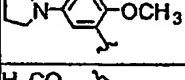
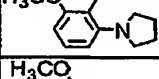
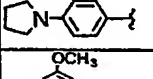



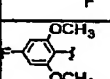

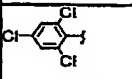

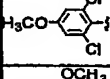
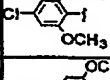
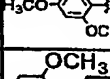
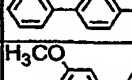
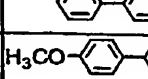
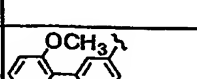


No.	R1	R2	R3	R4
A0589	CH3-		H	CH3
A0590	CH3-		H	CH3
A0591	CH3-		H	CH3
A0592	CH3-		H	CH3
A0593	CH3-		H	CH3
A0594	CH3-		H	CH3
A0595	CH3-		H	CH3
A0596	CH3-		H	CH3
A0597	CH3-		H	CH3
A0598	CH3-		H	CH3
A0599	CH3-		H	CH3
A0600	CH3-		H	CH3
A0601	CH3-		H	CH3
A0602	CH3-		H	CH3
A0603	CH3-		H	CH3
A0604	CH3-		H	CH3
A0605	CH3-		H	CH3
A0606	CH3-		H	CH3
A0607	CH3-		H	CH3
A0608	CH3-		H	CH3
A0609	CH3-		H	CH3

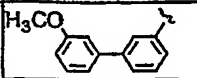
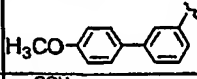
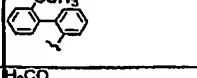
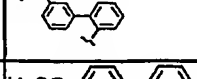
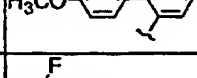
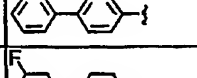
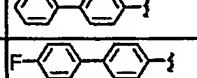

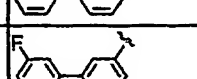
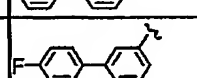
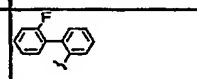
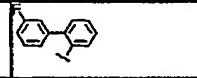
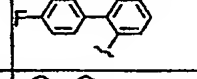
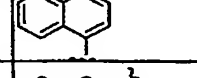
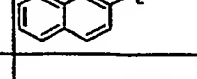
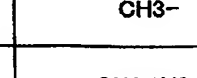
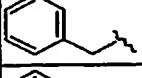
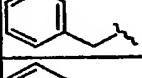
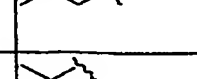
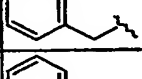
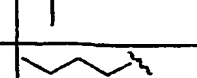
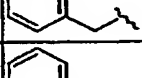

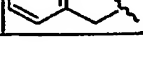
No.	R1	R2	R3	R4
A0610	CH ₃ -		H	CH ₃
A0611	CH ₃ -		H	CH ₃
A0612	CH ₃ -		H	CH ₃
A0613	CH ₃ -		H	CH ₃
A0614	CH ₃ -		H	CH ₃
A0615	CH ₃ -		H	CH ₃
A0616	CH ₃ -		H	CH ₃
A0617	CH ₃ -		H	CH ₃
A0618	CH ₃ -		H	CH ₃
A0619	CH ₃ -		H	CH ₃
A0620	CH ₃ -		H	CH ₃
A0621	CH ₃ -		H	CH ₃
A0622	CH ₃ -		H	CH ₃
A0623	CH ₃ -		H	CH ₃
A0624	CH ₃ -		H	CH ₃
A0625	CH ₃ -		H	CH ₃
A0626	CH ₃ -		H	CH ₃
A0627	CH ₃ -		H	CH ₃
A0628	CH ₃ -		H	CH ₃
A0629	CH ₃ -		H	CH ₃
A0630	CH ₃ -		H	CH ₃


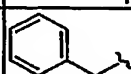

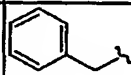

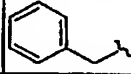

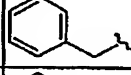
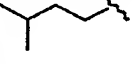
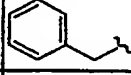

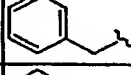
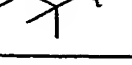
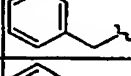

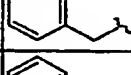
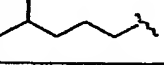
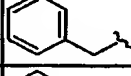

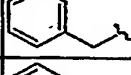
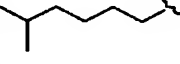
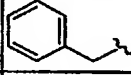

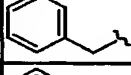

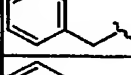
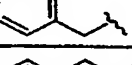
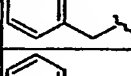
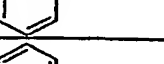
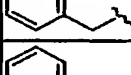
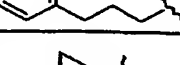
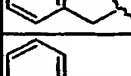



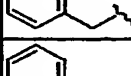

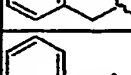

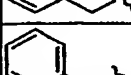

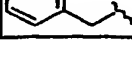
No.	R1	R2	R3	R4
A0631	CH3-		H	CH3
A0632	CH3-		H	CH3
A0633	CH3-		H	CH3
A0634	CH3-		H	CH3
A0635	CH3-		H	CH3
A0636	CH3-		H	CH3
A0637	CH3-		H	CH3
A0638	CH3-		H	CH3
A0639	CH3-		H	CH3
A0640	CH3-		H	CH3
A0641	CH3-		H	CH3
A0642	CH3-		H	CH3
A0643	CH3-		H	CH3
A0644	CH3-		H	CH3
A0645	CH3-		H	CH3
A0646	CH3-		H	CH3
A0647	CH3-		H	CH3
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







































No.	R1	R2	R3	R4
A0652	CH3-		H	CH3
A0653	CH3-		H	CH3
A0654	CH3-		H	CH3
A0655	CH3-		H	CH3
A0656	CH3-		H	CH3
A0657	CH3-		H	CH3
A0658	CH3-		H	CH3
A0659	CH3-		H	CH3
A0660	CH3-		H	CH3
A0661	CH3-		H	CH3
A0662	CH3-		H	CH3
A0663	CH3-		H	CH3
A0664	CH3-		H	CH3
A0665	CH3-		H	CH3
A0666	CH3-		H	CH3
A0667	CH3-		H	CH3
A0668	CH3-		H	CH3
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A0671	CH3-		H	CH3
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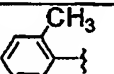
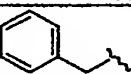
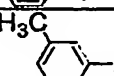
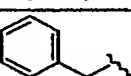
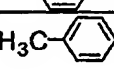
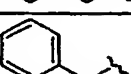
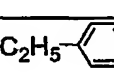
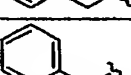
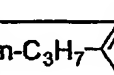

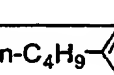
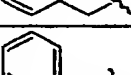
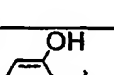
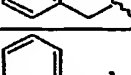
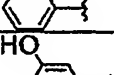
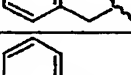
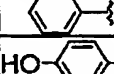
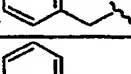
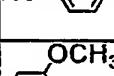
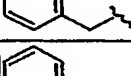
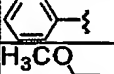
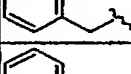
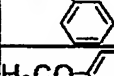
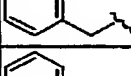
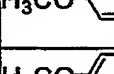
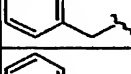
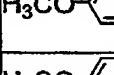
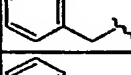
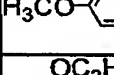
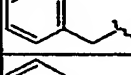
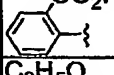
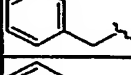
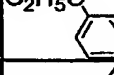
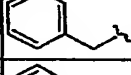
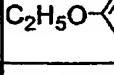
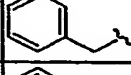
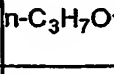
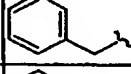
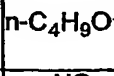
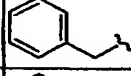
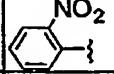
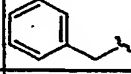
No.	R1	R2	R3	R4
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A0674	CH3-		H	CH3
A0675	CH3-		H	CH3
A0676	CH3-		H	CH3
A0677	CH3-		H	CH3
A0678	CH3-		H	CH3
A0679	CH3-		H	CH3
A0680	CH3-		H	CH3
A0681	CH3-		H	CH3
A0682	CH3-		H	CH3
A0683	CH3-		H	CH3
A0684	CH3-		H	CH3
A0685	CH3-		H	CH3
A0686	CH3-		H	CH3
A0687	CH3-		H	CH3
A0688	CH3-		H	CH3
A0689	CH3-		H	CH3
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A0691	CH3-		H	CH3
A0692	CH3-		H	CH3
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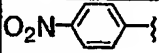
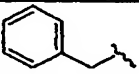
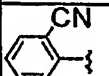
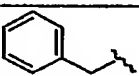
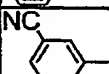
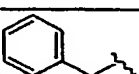
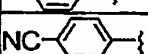
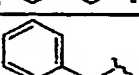
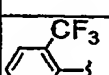
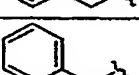
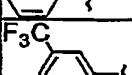

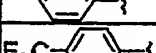

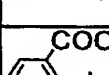
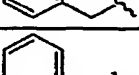
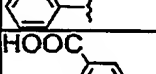
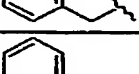
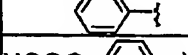
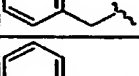
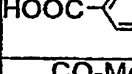
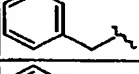
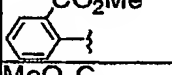
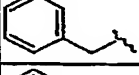

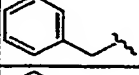
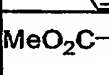
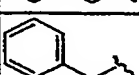
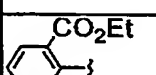
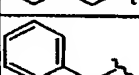
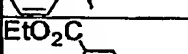
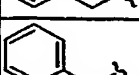
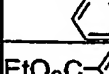
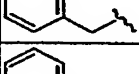
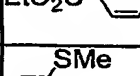
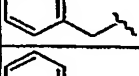
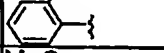
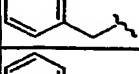
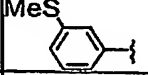
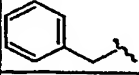
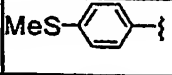
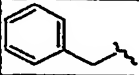
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A0695	CH3-		H	CH3
A0696	CH3-		H	CH3
A0697	CH3-		H	CH3
A0698	CH3-		H	CH3
A0699	CH3-		H	CH3
A0700	CH3-		H	CH3
A0701	CH3-		H	CH3
A0702	CH3-		H	CH3
A0703	CH3-		H	CH3
A0704	CH3-		H	CH3
A0705	CH3-		H	CH3
A0706	CH3-		H	CH3
A0707	CH3-		H	CH3
A0708	CH3-		H	CH3
A0709	CH3-		H	CH3
A0710	CH3-		H	CH3
A0711	CH3-		H	CH3
A0712	CH3-		H	CH3
A0713	CH3-		H	CH3
A0714	CH3-		H	CH3

No.	R1	R2	R3	R4
A0715	CH3-		H	CH3
A0716	CH3-		H	CH3
A0717	CH3-		H	CH3
A0718	CH3-		H	CH3
A0719	CH3-		H	CH3
A0720	CH3-		H	CH3
A0721	CH3-		H	CH3
A0722	CH3-		H	CH3
A0723	CH3-		H	CH3
A0724	CH3-		H	CH3
A0725	CH3-		H	CH3
A0726	CH3-		H	CH3
A0727	CH3-		H	CH3
A0728	CH3-		H	CH3
A0729	CH3-		H	CH3
A0730	CH3-		H	CH3
A0731	CH3-	CH3-	H	
A0732	CH3-	CH3CH2-	H	
A0733	CH3-		H	
A0734	CH3-		H	
A0735	CH3-		H	


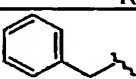

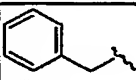
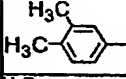
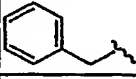

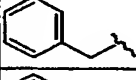

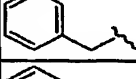
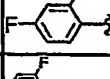
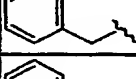

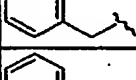

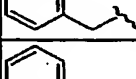
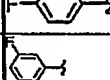
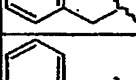

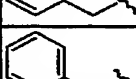
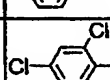
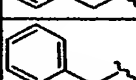
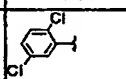
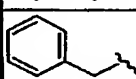

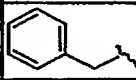

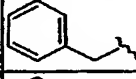
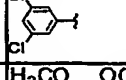
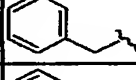

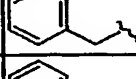
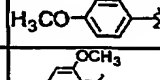
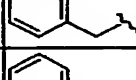
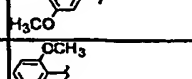
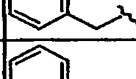
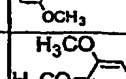
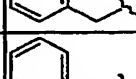

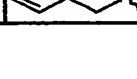


No.	R1	R2	R3	R4
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A0737	CH3-		H	
A0738	CH3-		H	
A0739	CH3-		H	
A0740	CH3-		H	
A0741	CH3-		H	
A0742	CH3-		H	
A0743	CH3-		H	
A0744	CH3-		H	
A0745	CH3-		H	
A0746	CH3-		H	
A0747	CH3-		H	
A0748	CH3-		H	
A0749	CH3-		H	
A0750	CH3-		H	
A0751	CH3-		H	
A0752	CH3-		H	
A0753	CH3-		H	
A0754	CH3-		H	
A0755	CH3-		H	
A0756	CH3-		H	


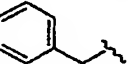

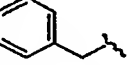

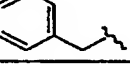

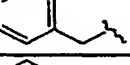

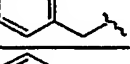

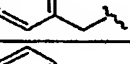

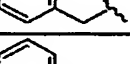







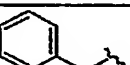

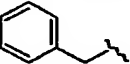

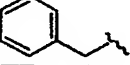

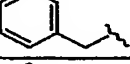

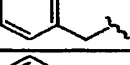

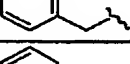

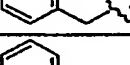





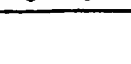


No.	R1	R2	R3	R4
A0757	CH3-		H	
A0758	CH3-		H	
A0759	CH3-		H	
A0760	CH3-		H	
A0761	CH3-		H	
A0762	CH3-		H	
A0763	CH3-		H	
A0764	CH3-		H	
A0765	CH3-		H	
A0766	CH3-		H	
A0767	CH3-		H	
A0768	CH3-		H	
A0769	CH3-		H	
A0770	CH3-		H	
A0771	CH3-		H	
A0772	CH3-		H	
A0773	CH3-		H	
A0774	CH3-		H	
A0775	CH3-		H	
A0776	CH3-		H	
A0777	CH3-		H	


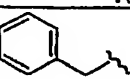
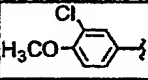
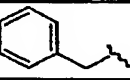
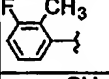
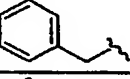
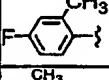
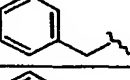
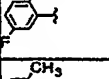
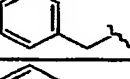
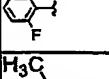
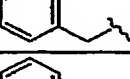
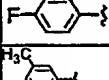
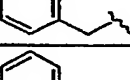
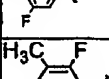
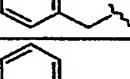
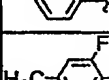
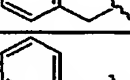
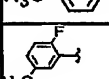
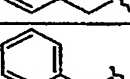
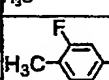
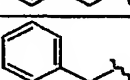
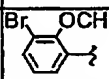
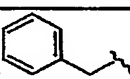
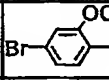
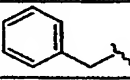
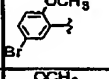
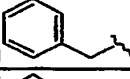
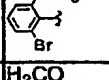
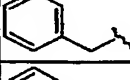
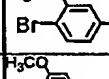
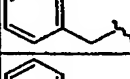
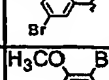
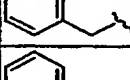
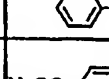
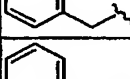
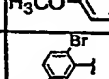
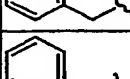
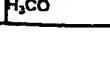
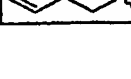


No.	R1	R2	R3	R4
A0778	CH ₃ -		H	
A0779	CH ₃ -		H	
A0780	CH ₃ -		H	
A0781	CH ₃ -		H	
A0782	CH ₃ -		H	
A0783	CH ₃ -		H	
A0784	CH ₃ -		H	
A0785	CH ₃ -		H	
A0786	CH ₃ -		H	
A0787	CH ₃ -		H	
A0788	CH ₃ -		H	
A0789	CH ₃ -		H	
A0790	CH ₃ -		H	
A0791	CH ₃ -		H	
A0792	CH ₃ -		H	
A0793	CH ₃ -		H	
A0794	CH ₃ -		H	
A0795	CH ₃ -		H	
A0796	CH ₃ -		H	
A0797	CH ₃ -		H	
A0798	CH ₃ -		H	

No.	R1	R2	R3	R4
A0799	CH ₃ -		H	
A0800	CH ₃ -		H	
A0801	CH ₃ -		H	
A0802	CH ₃ -		H	
A0803	CH ₃ -		H	
A0804	CH ₃ -		H	
A0805	CH ₃ -		H	
A0806	CH ₃ -		H	
A0807	CH ₃ -		H	
A0808	CH ₃ -		H	
A0809	CH ₃ -		H	
A0810	CH ₃ -		H	
A0811	CH ₃ -		H	
A0812	CH ₃ -		H	
A0813	CH ₃ -		H	
A0814	CH ₃ -		H	
A0815	CH ₃ -		H	
A0816	CH ₃ -		H	
A0817	CH ₃ -		H	
A0818	CH ₃ -		H	
A0819	CH ₃ -		H	

No.	R1	R2	R3	R4
A0820	CH3-		H	
A0821	CH3-		H	
A0822	CH3-		H	
A0823	CH3-		H	
A0824	CH3-		H	
A0825	CH3-		H	
A0826	CH3-		H	
A0827	CH3-		H	
A0828	CH3-		H	
A0829	CH3-		H	
A0830	CH3-		H	
A0831	CH3-		H	
A0832	CH3-		H	
A0833	CH3-		H	
A0834	CH3-		H	
A0835	CH3-		H	
A0836	CH3-		H	
A0837	CH3-		H	
A0838	CH3-		H	
A0839	CH3-		H	
A0840	CH3-		H	

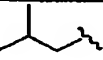

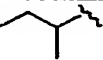





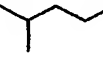

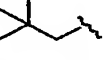



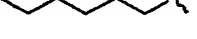

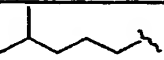



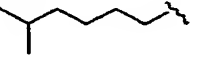



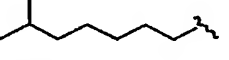

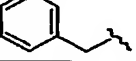

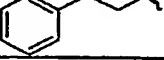

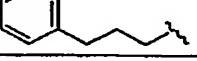











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A0844	CH3-		H	
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A0846	CH3-		H	
A0847	CH3-		H	
A0848	CH3-		H	
A0849	CH3-		H	
A0850	CH3-		H	
A0851	CH3-		H	
A0852	CH3-		H	
A0853	CH3-		H	
A0854	CH3-		H	
A0855	CH3-		H	
A0856	CH3-		H	
A0857	CH3-		H	
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









































No.	R1	R2	R3	R4
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A0863	CH3-		H	
A0864	CH3-		H	
A0865	CH3-		H	
A0866	CH3-		H	
A0867	CH3-		H	
A0868	CH3-		H	
A0869	CH3-		H	
A0870	CH3-		H	
A0871	CH3-		H	
A0872	CH3-		H	
A0873	CH3-		H	
A0874	CH3-		H	
A0875	CH3-		H	
A0876	CH3-		H	
A0877	CH3-		H	
A0878	CH3-		H	
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

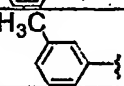

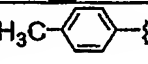

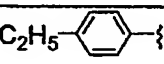

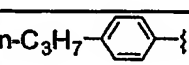

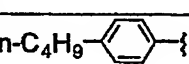



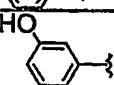

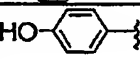



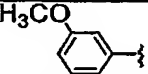

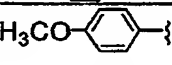

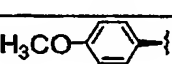

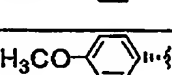

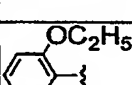

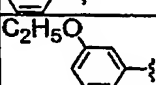

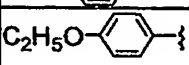

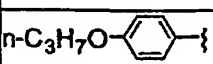

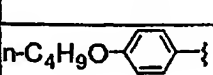



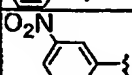

No.	R1	R2	R3	R4
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A0886	CH3-		H	
A0887	CH3-		H	
A0888	CH3-		H	
A0889	CH3-		H	
A0890	CH3-		H	
A0891	CH3-		H	
A0892	CH3-		H	
A0893	CH3-		H	
A0894	CH3-		H	
A0895	CH3-		H	
A0896	CH3-		H	
A0897	CH3-		H	
A0898	CH3-		H	
A0899	CH3-		H	
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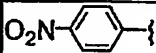



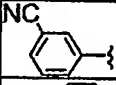

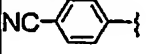



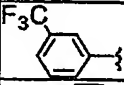

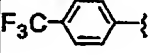



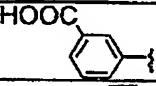

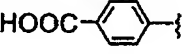

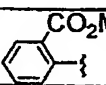

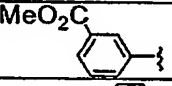

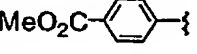

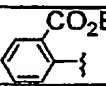

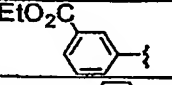

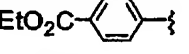

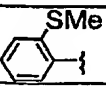

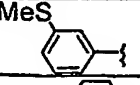

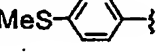

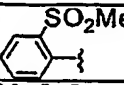

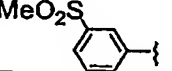

No.	R1	R2	R3	R4
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A0905	CH3-		H	
A0906	CH3-		H	
A0907	CH3-		H	
A0908	CH3-		H	
A0909	CH3-		H	
A0910	CH3-		H	
A0911	CH3-		H	
A0912	CH3-		H	
A0913	CH3-		H	
A0914	CH3-		H	
A0915	CH3-		H	
A0916	CH3-		H	
A0917	CH3-		H	
A0918	CH3-		H	
A0919	CH3-		H	
A0920	CH3-		H	
A0921	CH3-		H	
A0922	CH3-		H	
A0923	CH3-		H	
A0924	CH3-		H	

No.	R1	R2	R3	R4
A0925	CH3-		H	
A0926	CH3-		H	
A0927	CH3-		H	
A0928	CH3-		H	
A0929	CH3-		H	
A0930	CH3-		H	
A0931	CH3-		H	
A0932	CH3-		H	
A0933	CH3-		H	
A0934	CH3-		H	
A0935	CH3-		H	
A0936	CH3-		H	
A0937	CH3-		H	
A0938	CH3-		H	
A0939	CH3-		H	
A0940	CH3-		H	
A0941	CH3-	CH3-	H	
A0942	CH3-	CH3CH2-	H	
A0943	CH3-		H	
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



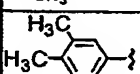





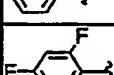





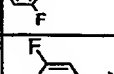





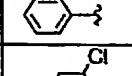





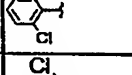



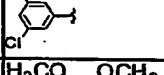

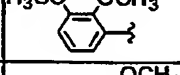

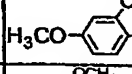



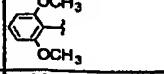

No.	R1	R2	R3	R4
A0946	CH3-		H	
A0947	CH3-		H	
A0948	CH3-		H	
A0949	CH3-		H	
A0950	CH3-		H	
A0951	CH3-		H	
A0952	CH3-		H	
A0953	CH3-		H	
A0954	CH3-		H	
A0955	CH3-		H	
A0956	CH3-		H	
A0957	CH3-		H	
A0958	CH3-		H	
A0959	CH3-		H	
A0960	CH3-		H	
A0961	CH3-		H	
A0962	CH3-		H	
A0963	CH3-		H	
A0964	CH3-		H	
A0965	CH3-		H	
A0966	CH3-		H	











































No.	R1	R2	R3	R4
A0967	CH3-		H	
A0968	CH3-		H	
A0969	CH3-		H	
A0970	CH3-		H	
A0971	CH3-		H	
A0972	CH3-		H	
A0973	CH3-		H	
A0974	CH3-		H	
A0975	CH3-		H	
A0976	CH3-		H	
A0977	CH3-		H	
A0978	CH3-		H	
A0979	CH3-		H	
A0980	CH3-		H	
A0981	CH3-		H	
A0982	CH3-		H	
A0983	CH3-		H	
A0984	CH3-		H	
A0985	CH3-		H	
A0986	CH3-		H	
A0987	CH3-		H	

No.	R1	R2	R3	R4
A0988	CH ₃ -		H	
A0989	CH ₃ -		H	
A0990	CH ₃ -		H	
A0991	CH ₃ -		H	
A0992	CH ₃ -		H	
A0993	CH ₃ -		H	
A0994	CH ₃ -		H	
A0995	CH ₃ -		H	
A0996	CH ₃ -		H	
A0997	CH ₃ -		H	
A0998	CH ₃ -		H	
A0999	CH ₃ -		H	
A1000	CH ₃ -		H	
A1001	CH ₃ -		H	
A1002	CH ₃ -		H	
A1003	CH ₃ -		H	
A1004	CH ₃ -		H	
A1005	CH ₃ -		H	
A1006	CH ₃ -		H	
A1007	CH ₃ -		H	
A1008	CH ₃ -		H	

No.	R1	R2	R3	R4
A1009	CH ₃ -		H	
A1010	CH ₃ -		H	
A1011	CH ₃ -		H	
A1012	CH ₃ -		H	
A1013	CH ₃ -		H	
A1014	CH ₃ -		H	
A1015	CH ₃ -		H	
A1016	CH ₃ -		H	
A1017	CH ₃ -		H	
A1018	CH ₃ -		H	
A1019	CH ₃ -		H	
A1020	CH ₃ -		H	
A1021	CH ₃ -		H	
A1022	CH ₃ -		H	
A1023	CH ₃ -		H	
A1024	CH ₃ -		H	
A1025	CH ₃ -		H	
A1026	CH ₃ -		H	
A1027	CH ₃ -		H	
A1028	CH ₃ -		H	
A1029	CH ₃ -		H	

No.	R1	R2	R3	R4
A1030	CH ₃ -		H	
A1031	CH ₃ -		H	
A1032	CH ₃ -		H	
A1033	CH ₃ -		H	
A1034	CH ₃ -		H	
A1035	CH ₃ -		H	
A1036	CH ₃ -		H	
A1037	CH ₃ -		H	
A1038	CH ₃ -		H	
A1039	CH ₃ -		H	
A1040	CH ₃ -		H	
A1041	CH ₃ -		H	
A1042	CH ₃ -		H	
A1043	CH ₃ -		H	
A1044	CH ₃ -		H	
A1045	CH ₃ -		H	
A1046	CH ₃ -		H	
A1047	CH ₃ -		H	
A1048	CH ₃ -		H	
A1049	CH ₃ -		H	
A1050	CH ₃ -		H	



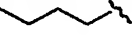
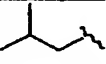


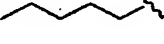
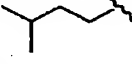
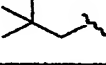


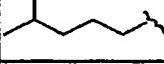

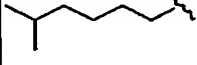

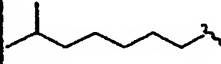
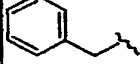
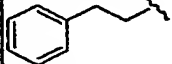
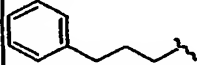


No.	R1	R2	R3	R4
A1051	CH3-		H	
A1052	CH3-		H	
A1053	CH3-		H	
A1054	CH3-		H	
A1055	CH3-		H	
A1056	CH3-		H	
A1057	CH3-		H	
A1058	CH3-		H	
A1059	CH3-		H	
A1060	CH3-		H	
A1061	CH3-		H	
A1062	CH3-		H	
A1063	CH3-		H	
A1064	CH3-		H	
A1065	CH3-		H	
A1066	CH3-		H	
A1067	CH3-		H	
A1068	CH3-		H	
A1069	CH3-		H	
A1070	CH3-		H	
A1071	CH3-		H	


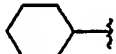
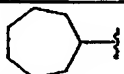






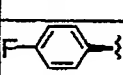
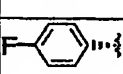

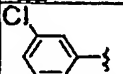
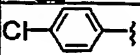
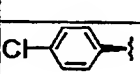
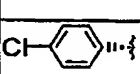

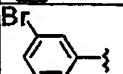
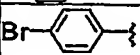
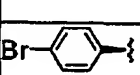
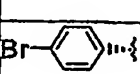
No.	R1	R2	R3	R4
A1072	CH3-		H	
A1073	CH3-		H	
A1074	CH3-		H	
A1075	CH3-		H	
A1076	CH3-		H	
A1077	CH3-		H	
A1078	CH3-		H	
A1079	CH3-		H	
A1080	CH3-		H	
A1081	CH3-		H	
A1082	CH3-		H	
A1083	CH3-		H	
A1084	CH3-		H	
A1085	CH3-		H	
A1086	CH3-		H	
A1087	CH3-		H	
A1088	CH3-		H	
A1089	CH3-		H	
A1090	CH3-		H	
A1091	CH3-		H	
A1092	CH3-		H	






















No.	R1	R2	R3	R4
A1093	CH3-		H	
A1094	CH3-		H	
A1095	CH3-		H	
A1096	CH3-		H	
A1097	CH3-		H	
A1098	CH3-		H	
A1099	CH3-		H	
A1100	CH3-		H	
A1101	CH3-		H	
A1102	CH3-		H	
A1103	CH3-		H	
A1104	CH3-		H	
A1105	CH3-		H	
A1106	CH3-		H	
A1107	CH3-		H	
A1108	CH3-		H	
A1109	CH3-		H	
A1110	CH3-		H	
A1111	CH3-		H	
A1112	CH3-		H	
A1113	CH3-		H	

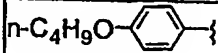

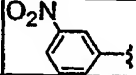
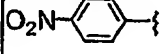

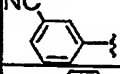
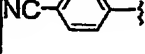

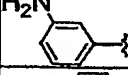
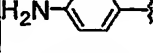

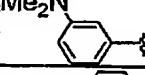
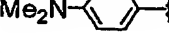
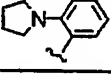
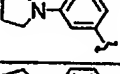
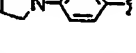
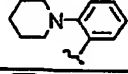
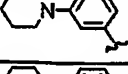
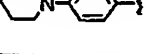
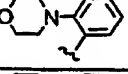
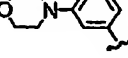
No.	R1	R2	R3	R4
A1114	CH3-		H	
A1115	CH3-		H	
A1116	CH3-		H	
A1117	CH3-		H	
A1118	CH3-		H	
A1119	CH3-		H	
A1120	CH3-		H	
A1121	CH3-		H	
A1122	CH3-		H	
A1123	CH3-		H	
A1124	CH3-		H	
A1125	CH3-		H	
A1126	CH3-		H	
A1127	CH3-		H	
A1128	CH3-		H	
A1129	CH3-		H	
A1130	CH3-		H	
A1131	CH3-		H	
A1132	CH3-		H	
A1133	CH3-		H	
A1134	CH3-		H	

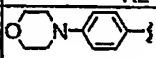
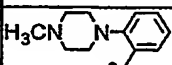

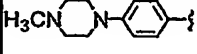
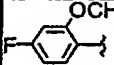
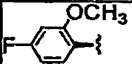
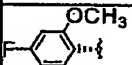

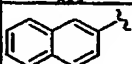
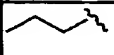

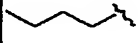
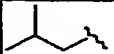
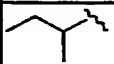


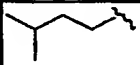
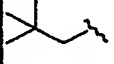

No.	R1	R2	R3	R4
A1135	CH3-		H	
A1136	CH3-		H	
A1137	CH3-		H	
A1138	CH3-		H	
A1139	CH3-		H	
A1140	CH3-		H	
A1141	CH3-		H	
A1142	CH3-		H	
A1143	CH3-		H	
A1144	CH3-		H	
A1145	CH3-		H	
A1146	CH3-		H	
A1147	CH3-		H	
A1148	CH3-		H	
A1149	CH3-		H	
A1150	CH3-		H	
A1151	CH3-		H	
A1152	CH3-		H	
A1153	CH3-		H	
A1154	CH3-	CH3-	CH3-	H
A1155	CH3-	CH3CH2-	CH3-	H


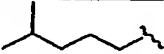

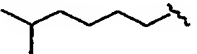

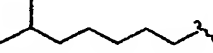
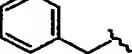
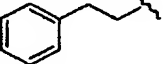
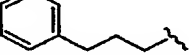




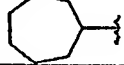






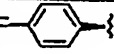
No.	R1	R2	R3	R4
A1156	CH3-		CH3-	H
A1157	CH3-		CH3-	H
A1158	CH3-		CH3-	H
A1159	CH3-		CH3-	H
A1160	CH3-		CH3-	H
A1161	CH3-		CH3-	H
A1162	CH3-		CH3-	H
A1163	CH3-		CH3-	H
A1164	CH3-		CH3-	H
A1165	CH3-		CH3-	H
A1166	CH3-		CH3-	H
A1167	CH3-		CH3-	H
A1168	CH3-		CH3-	H
A1169	CH3-		CH3-	H
A1170	CH3-		CH3-	H
A1171	CH3-		CH3-	H
A1172	CH3-		CH3-	H
A1173	CH3-		CH3-	H
A1174	CH3-		CH3-	H
A1175	CH3-		CH3-	H
A1176	CH3-		CH3-	H

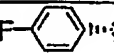
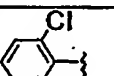
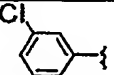
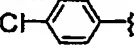

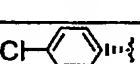
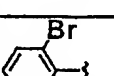
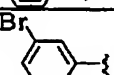
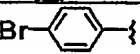
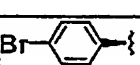
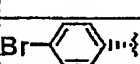
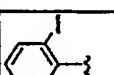
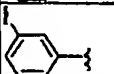
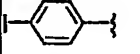
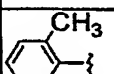
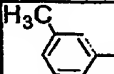
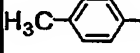
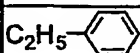
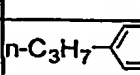
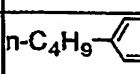
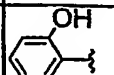
No.	R1	R2	R3	R4
A1177	CH3-		CH3-	H
A1178	CH3-		CH3-	H
A1179	CH3-		CH3-	H
A1180	CH3-		CH3-	H
A1181	CH3-		CH3-	H
A1182	CH3-		CH3-	H
A1183	CH3-		CH3-	H
A1184	CH3-		CH3-	H
A1185	CH3-		CH3-	H
A1186	CH3-		CH3-	H
A1187	CH3-		CH3-	H
A1188	CH3-		CH3-	H
A1189	CH3-		CH3-	H
A1190	CH3-		CH3-	H
A1191	CH3-		CH3-	H
A1192	CH3-		CH3-	H
A1193	CH3-		CH3-	H
A1194	CH3-		CH3-	H
A1195	CH3-		CH3-	H
A1196	CH3-		CH3-	H
A1197	CH3-		CH3-	H

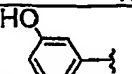


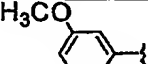
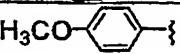
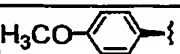
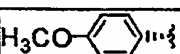
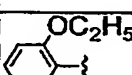
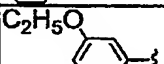
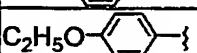
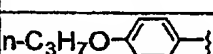
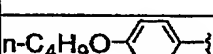

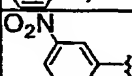
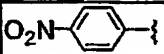

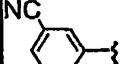
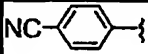

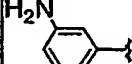
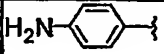
No.	R1	R2	R3	R4
A1198	CH ₃ -		CH ₃ -	H
A1199	CH ₃ -		CH ₃ -	H
A1200	CH ₃ -		CH ₃ -	H
A1201	CH ₃ -		CH ₃ -	H
A1202	CH ₃ -		CH ₃ -	H
A1203	CH ₃ -		CH ₃ -	H
A1204	CH ₃ -		CH ₃ -	H
A1205	CH ₃ -		CH ₃ -	H
A1206	CH ₃ -		CH ₃ -	H
A1207	CH ₃ -		CH ₃ -	H
A1208	CH ₃ -		CH ₃ -	H
A1209	CH ₃ -		CH ₃ -	H
A1210	CH ₃ -		CH ₃ -	H
A1211	CH ₃ -		CH ₃ -	H
A1212	CH ₃ -		CH ₃ -	H
A1213	CH ₃ -		CH ₃ -	H
A1214	CH ₃ -		CH ₃ -	H
A1215	CH ₃ -		CH ₃ -	H
A1216	CH ₃ -		CH ₃ -	H
A1217	CH ₃ -		CH ₃ -	H
A1218	CH ₃ -		CH ₃ -	H





















No.	R1	R2	R3	R4
A1219	CH3-		CH3-	H
A1220	CH3-		CH3-	H
A1221	CH3-		CH3-	H
A1222	CH3-		CH3-	H
A1223	CH3-		CH3-	H
A1224	CH3-		CH3-	H
A1225	CH3-		CH3-	H
A1226	CH3-		CH3-	H
A1227	CH3-		CH3-	H
A1228	CH3-		CH3-	H
A1229	CH3-		CH3-	H
A1230	CH3-		CH3-	H
A1231	CH3-		CH3-	H
A1232	CH3-		CH3-	H
A1233	CH3-		CH3-	H
A1234	CH3-		CH3-	H
A1235	CH3-		CH3-	H
A1236	CH3-		CH3-	H
A1237	CH3-		CH3-	H
A1238	CH3-		CH3-	H
A1239	CH3-		CH3-	H




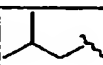



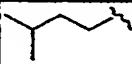
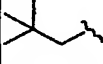


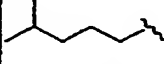

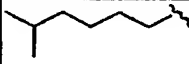

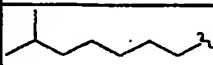
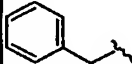
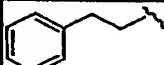


No.	R1	R2	R3	R4
A1240	CH ₃ -		CH ₃ -	H
A1241	CH ₃ -		CH ₃ -	H
A1242	CH ₃ -		CH ₃ -	H
A1243	CH ₃ -		CH ₃ -	H
A1244	CH ₃ -		CH ₃ -	H
A1245	CH ₃ -		CH ₃ -	H
A1246	CH ₃ -		CH ₃ -	H
A1247	CH ₃ -		CH ₃ -	H
A1248	CH ₃ -		CH ₃ -	H
A1249	CH ₃ -	CH ₃ -	H	CH ₃ -
A1250	CH ₃ -	CH ₃ CH ₂ -	H	CH ₃ -
A1251	CH ₃ -		H	CH ₃ -
A1252	CH ₃ -		H	CH ₃ -
A1253	CH ₃ -		H	CH ₃ -
A1254	CH ₃ -		H	CH ₃ -
A1255	CH ₃ -		H	CH ₃ -
A1256	CH ₃ -		H	CH ₃ -
A1257	CH ₃ -		H	CH ₃ -
A1258	CH ₃ -		H	CH ₃ -
A1259	CH ₃ -		H	CH ₃ -
A1260	CH ₃ -		H	CH ₃ -


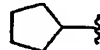
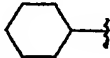
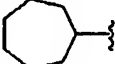










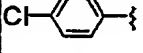
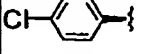
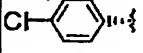


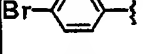
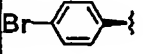
No.	R1	R2	R3	R4
A1261	CH3-		H	CH3-
A1262	CH3-		H	CH3-
A1263	CH3-		H	CH3-
A1264	CH3-		H	CH3-
A1265	CH3-		H	CH3-
A1266	CH3-		H	CH3-
A1267	CH3-		H	CH3-
A1268	CH3-		H	CH3-
A1269	CH3-		H	CH3-
A1270	CH3-		H	CH3-
A1271	CH3-		H	CH3-
A1272	CH3-		H	CH3-
A1273	CH3-		H	CH3-
A1274	CH3-		H	CH3-
A1275	CH3-		H	CH3-
A1276	CH3-		H	CH3-
A1277	CH3-		H	CH3-
A1278	CH3-		H	CH3-
A1279	CH3-		H	CH3-
A1280	CH3-		H	CH3-
A1281	CH3-		H	CH3-

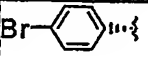
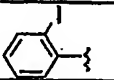


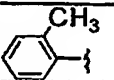
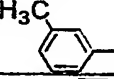
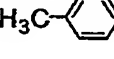
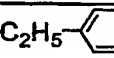
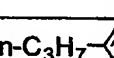
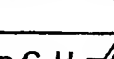
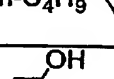
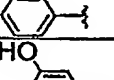
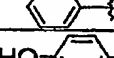
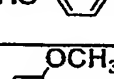
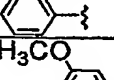
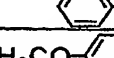
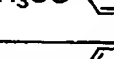
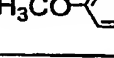
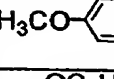
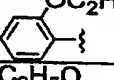

No.	R1	R2	R3	R4
A1282	CH ₃ -		H	CH ₃ -
A1283	CH ₃ -		H	CH ₃ -
A1284	CH ₃ -		H	CH ₃ -
A1285	CH ₃ -		H	CH ₃ -
A1286	CH ₃ -		H	CH ₃ -
A1287	CH ₃ -		H	CH ₃ -
A1288	CH ₃ -		H	CH ₃ -
A1289	CH ₃ -		H	CH ₃ -
A1290	CH ₃ -		H	CH ₃ -
A1291	CH ₃ -		H	CH ₃ -
A1292	CH ₃ -		H	CH ₃ -
A1293	CH ₃ -		H	CH ₃ -
A1294	CH ₃ -		H	CH ₃ -
A1295	CH ₃ -		H	CH ₃ -
A1296	CH ₃ -		H	CH ₃ -
A1297	CH ₃ -		H	CH ₃ -
A1298	CH ₃ -		H	CH ₃ -
A1299	CH ₃ -		H	CH ₃ -
A1300	CH ₃ -		H	CH ₃ -
A1301	CH ₃ -		H	CH ₃ -
A1302	CH ₃ -		H	CH ₃ -

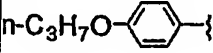
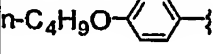

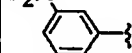
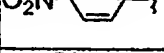


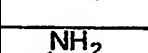

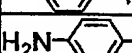
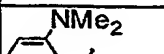

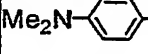
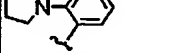

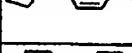


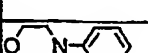
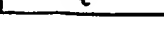

No.	R1	R2	R3	R4
A1303	CH ₃ -		H	CH ₃ -
A1304	CH ₃ -		H	CH ₃ -
A1305	CH ₃ -		H	CH ₃ -
A1306	CH ₃ -		H	CH ₃ -
A1307	CH ₃ -		H	CH ₃ -
A1308	CH ₃ -		H	CH ₃ -
A1309	CH ₃ -		H	CH ₃ -
A1310	CH ₃ -		H	CH ₃ -
A1311	CH ₃ -		H	CH ₃ -
A1312	CH ₃ -		H	CH ₃ -
A1313	CH ₃ -		H	CH ₃ -
A1314	CH ₃ -		H	CH ₃ -
A1315	CH ₃ -		H	CH ₃ -
A1316	CH ₃ -		H	CH ₃ -
A1317	CH ₃ -		H	CH ₃ -
A1318	CH ₃ -		H	CH ₃ -
A1319	CH ₃ -		H	CH ₃ -
A1320	CH ₃ -		H	CH ₃ -
A1321	CH ₃ -		H	CH ₃ -
A1322	CH ₃ -		H	CH ₃ -
A1323	CH ₃ -		H	CH ₃ -

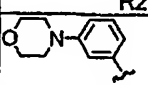
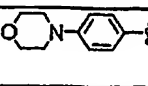
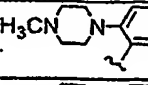
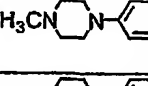
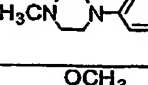
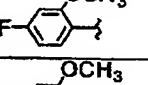
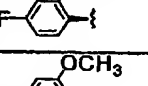
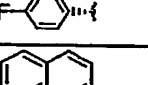
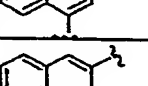
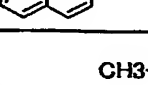
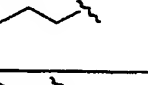

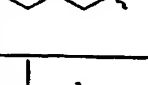
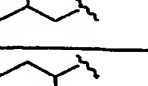
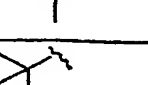
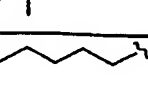
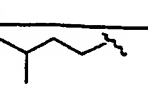
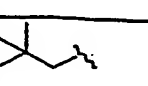

No.	R1	R2	R3	R4
A1324	CH3-		H	CH3-
A1325	CH3-		H	CH3-
A1326	CH3-		H	CH3-
A1327	CH3-		H	CH3-
A1328	CH3-		H	CH3-
A1329	CH3-		H	CH3-
A1330	CH3-		H	CH3-
A1331	CH3-		H	CH3-
A1332	CH3-		H	CH3-
A1333	CH3-		H	CH3-
A1334	CH3-		H	CH3-
A1335	CH3-		H	CH3-
A1336	CH3-		H	CH3-
A1337	CH3-		H	CH3-
A1338	CH3-		H	CH3-
A1339	CH3-		H	CH3-
A1340	CH3-		H	CH3-
A1341	CH3-		H	CH3-
A1342	CH3-		H	CH3-
A1343	CH3-		H	CH3-
A1344	CH3CH2-	CH3-	H	H



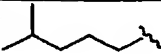

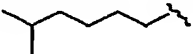


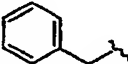
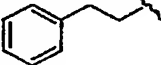
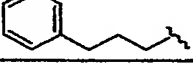



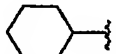
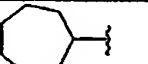






No.	R1	R2	R3	R4
A1345	CH ₃ CH ₂ -	CH ₃ CH ₂ -	H	H
A1346	CH ₃ CH ₂ -		H	H
A1347	CH ₃ CH ₂ -		H	H
A1348	CH ₃ CH ₂ -		H	H
A1349	CH ₃ CH ₂ -		H	H
A1350	CH ₃ CH ₂ -		H	H
A1351	CH ₃ CH ₂ -		H	H
A1352	CH ₃ CH ₂ -		H	H
A1353	CH ₃ CH ₂ -		H	H
A1354	CH ₃ CH ₂ -		H	H
A1355	CH ₃ CH ₂ -		H	H
A1356	CH ₃ CH ₂ -		H	H
A1357	CH ₃ CH ₂ -		H	H
A1358	CH ₃ CH ₂ -		H	H
A1359	CH ₃ CH ₂ -		H	H
A1360	CH ₃ CH ₂ -		H	H
A1361	CH ₃ CH ₂ -		H	H
A1362	CH ₃ CH ₂ -		H	H
A1363	CH ₃ CH ₂ -		H	H
A1364	CH ₃ CH ₂ -		H	H
A1365	CH ₃ CH ₂ -		H	H


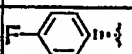
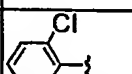
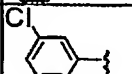
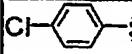
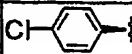

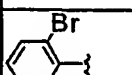
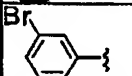
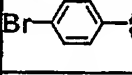
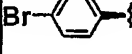
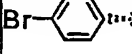
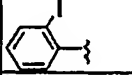
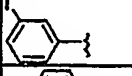
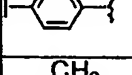
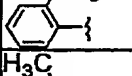
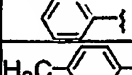
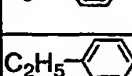
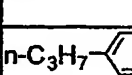
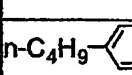
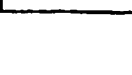
No.	R1	R2	R3	R4
A1366	CH ₃ CH ₂ -		H	H
A1367	CH ₃ CH ₂ -		H	H
A1368	CH ₃ CH ₂ -		H	H
A1369	CH ₃ CH ₂ -		H	H
A1370	CH ₃ CH ₂ -		H	H
A1371	CH ₃ CH ₂ -		H	H
A1372	CH ₃ CH ₂ -		H	H
A1373	CH ₃ CH ₂ -		H	H
A1374	CH ₃ CH ₂ -		H	H
A1375	CH ₃ CH ₂ -		H	H
A1376	CH ₃ CH ₂ -		H	H
A1377	CH ₃ CH ₂ -		H	H
A1378	CH ₃ CH ₂ -		H	H
A1379	CH ₃ CH ₂ -		H	H
A1380	CH ₃ CH ₂ -		H	H
A1381	CH ₃ CH ₂ -		H	H
A1382	CH ₃ CH ₂ -		H	H
A1383	CH ₃ CH ₂ -		H	H
A1384	CH ₃ CH ₂ -		H	H
A1385	CH ₃ CH ₂ -		H	H
A1386	CH ₃ CH ₂ -		H	H



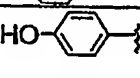


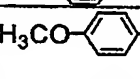
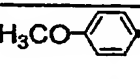
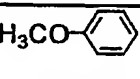


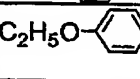
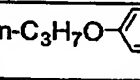
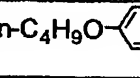


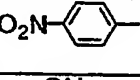


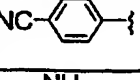


No.	R1	R2	R3	R4
A1387	CH ₃ CH ₂ -		H	H
A1388	CH ₃ CH ₂ -		H	H
A1389	CH ₃ CH ₂ -		H	H
A1390	CH ₃ CH ₂ -		H	H
A1391	CH ₃ CH ₂ -		H	H
A1392	CH ₃ CH ₂ -		H	H
A1393	CH ₃ CH ₂ -		H	H
A1394	CH ₃ CH ₂ -		H	H
A1395	CH ₃ CH ₂ -		H	H
A1396	CH ₃ CH ₂ -		H	H
A1397	CH ₃ CH ₂ -		H	H
A1398	CH ₃ CH ₂ -		H	H
A1399	CH ₃ CH ₂ -		H	H
A1400	CH ₃ CH ₂ -		H	H
A1401	CH ₃ CH ₂ -		H	H
A1402	CH ₃ CH ₂ -		H	H
A1403	CH ₃ CH ₂ -		H	H
A1404	CH ₃ CH ₂ -		H	H
A1405	CH ₃ CH ₂ -		H	H
A1406	CH ₃ CH ₂ -		H	H
A1407	CH ₃ CH ₂ -		H	H

No.	R1	R2	R3	R4
A1408	CH ₃ CH ₂ -		H	H
A1409	CH ₃ CH ₂ -		H	H
A1410	CH ₃ CH ₂ -		H	H
A1411	CH ₃ CH ₂ -		H	H
A1412	CH ₃ CH ₂ -		H	H
A1413	CH ₃ CH ₂ -		H	H
A1414	CH ₃ CH ₂ -		H	H
A1415	CH ₃ CH ₂ -		H	H
A1416	CH ₃ CH ₂ -		H	H
A1417	CH ₃ CH ₂ -		H	H
A1418	CH ₃ CH ₂ -		H	H
A1419	CH ₃ CH ₂ -		H	H
A1420	CH ₃ CH ₂ -		H	H
A1421	CH ₃ CH ₂ -		H	H
A1422	CH ₃ CH ₂ -		H	H
A1423	CH ₃ CH ₂ -		H	H
A1424	CH ₃ CH ₂ -		H	H
A1425	CH ₃ CH ₂ -		H	H
A1426	CH ₃ CH ₂ -		H	H
A1427	CH ₃ CH ₂ -		H	H
A1428	CH ₃ CH ₂ -		H	H

No.	R1	R2	R3	R4
A1429	CH ₃ CH ₂ -		H	H
A1430	CH ₃ CH ₂ -		H	H
A1431	CH ₃ CH ₂ -		H	H
A1432	CH ₃ CH ₂ -		H	H
A1433	CH ₃ CH ₂ -		H	H
A1434	CH ₃ CH ₂ -		H	H
A1435	CH ₃ CH ₂ -		H	H
A1436	CH ₃ CH ₂ -		H	H
A1437	CH ₃ CH ₂ -		H	H
A1438	CH ₃ CH ₂ -		H	H
A1439	CH ₃ CH ₂ -	CH ₃ -	H	CH ₃ -
A1440	CH ₃ CH ₂ -	CH ₃ CH ₂ -	H	CH ₃ -
A1441	CH ₃ CH ₂ -		H	CH ₃ -
A1442	CH ₃ CH ₂ -		H	CH ₃ -
A1443	CH ₃ CH ₂ -		H	CH ₃ -
A1444	CH ₃ CH ₂ -		H	CH ₃ -
A1445	CH ₃ CH ₂ -		H	CH ₃ -
A1446	CH ₃ CH ₂ -		H	CH ₃ -
A1447	CH ₃ CH ₂ -		H	CH ₃ -
A1448	CH ₃ CH ₂ -		H	CH ₃ -
A1449	CH ₃ CH ₂ -		H	CH ₃ -

No.	R1	R2	R3	R4
A1450	CH ₃ CH ₂ -		H	CH ₃ -
A1451	CH ₃ CH ₂ -		H	CH ₃ -
A1452	CH ₃ CH ₂ -		H	CH ₃ -
A1453	CH ₃ CH ₂ -		H	CH ₃ -
A1454	CH ₃ CH ₂ -		H	CH ₃ -
A1455	CH ₃ CH ₂ -		H	CH ₃ -
A1456	CH ₃ CH ₂ -		H	CH ₃ -
A1457	CH ₃ CH ₂ -		H	CH ₃ -
A1458	CH ₃ CH ₂ -		H	CH ₃ -
A1459	CH ₃ CH ₂ -		H	CH ₃ -
A1460	CH ₃ CH ₂ -		H	CH ₃ -
A1461	CH ₃ CH ₂ -		H	CH ₃ -
A1462	CH ₃ CH ₂ -		H	CH ₃ -
A1463	CH ₃ CH ₂ -		H	CH ₃ -
A1464	CH ₃ CH ₂ -		H	CH ₃ -
A1465	CH ₃ CH ₂ -		H	CH ₃ -
A1466	CH ₃ CH ₂ -		H	CH ₃ -
A1467	CH ₃ CH ₂ -		H	CH ₃ -
A1468	CH ₃ CH ₂ -		H	CH ₃ -
A1469	CH ₃ CH ₂ -		H	CH ₃ -
A1470	CH ₃ CH ₂ -		H	CH ₃ -

No.	R1	R2	R3	R4
A1471	CH ₃ CH ₂ -		H	CH ₃ -
A1472	CH ₃ CH ₂ -		H	CH ₃ -
A1473	CH ₃ CH ₂ -		H	CH ₃ -
A1474	CH ₃ CH ₂ -		H	CH ₃ -
A1475	CH ₃ CH ₂ -		H	CH ₃ -
A1476	CH ₃ CH ₂ -		H	CH ₃ -
A1477	CH ₃ CH ₂ -		H	CH ₃ -
A1478	CH ₃ CH ₂ -		H	CH ₃ -
A1479	CH ₃ CH ₂ -		H	CH ₃ -
A1480	CH ₃ CH ₂ -		H	CH ₃ -
A1481	CH ₃ CH ₂ -		H	CH ₃ -
A1482	CH ₃ CH ₂ -		H	CH ₃ -
A1483	CH ₃ CH ₂ -		H	CH ₃ -
A1484	CH ₃ CH ₂ -		H	CH ₃ -
A1485	CH ₃ CH ₂ -		H	CH ₃ -
A1486	CH ₃ CH ₂ -		H	CH ₃ -
A1487	CH ₃ CH ₂ -		H	CH ₃ -
A1488	CH ₃ CH ₂ -		H	CH ₃ -
A1489	CH ₃ CH ₂ -		H	CH ₃ -
A1490	CH ₃ CH ₂ -		H	CH ₃ -
A1491	CH ₃ CH ₂ -		H	CH ₃ -

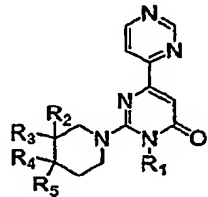






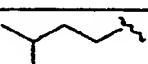



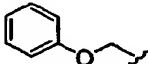
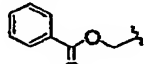
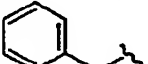
No.	R1	R2	R3	R4
A1492	CH ₃ CH ₂ -		H	CH ₃ -
A1493	CH ₃ CH ₂ -		H	CH ₃ -
A1494	CH ₃ CH ₂ -		H	CH ₃ -
A1495	CH ₃ CH ₂ -		H	CH ₃ -
A1496	CH ₃ CH ₂ -		H	CH ₃ -
A1497	CH ₃ CH ₂ -		H	CH ₃ -
A1498	CH ₃ CH ₂ -		H	CH ₃ -
A1499	CH ₃ CH ₂ -		H	CH ₃ -
A1500	CH ₃ CH ₂ -		H	CH ₃ -
A1501	CH ₃ CH ₂ -		H	CH ₃ -
A1502	CH ₃ CH ₂ -		H	CH ₃ -
A1503	CH ₃ CH ₂ -		H	CH ₃ -
A1504	CH ₃ CH ₂ -		H	CH ₃ -
A1505	CH ₃ CH ₂ -		H	CH ₃ -
A1506	CH ₃ CH ₂ -		H	CH ₃ -
A1507	CH ₃ CH ₂ -		H	CH ₃ -
A1508	CH ₃ CH ₂ -		H	CH ₃ -
A1509	CH ₃ CH ₂ -		H	CH ₃ -
A1510	CH ₃ CH ₂ -		H	CH ₃ -
A1511	CH ₃ CH ₂ -		H	CH ₃ -
A1512	CH ₃ CH ₂ -		H	CH ₃ -

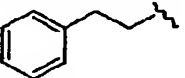
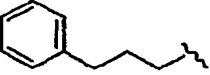













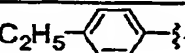



No.	R1	R2	R3	R4
A1513	CH ₃ CH ₂ -		H	CH ₃ -
A1514	CH ₃ CH ₂ -		H	CH ₃ -
A1515	CH ₃ CH ₂ -		H	CH ₃ -
A1516	CH ₃ CH ₂ -		H	CH ₃ -
A1517	CH ₃ CH ₂ -		H	CH ₃ -
A1518	CH ₃ CH ₂ -		H	CH ₃ -
A1519	CH ₃ CH ₂ -		H	CH ₃ -
A1520	CH ₃ CH ₂ -		H	CH ₃ -
A1521	CH ₃ CH ₂ -		H	CH ₃ -
A1522	CH ₃ CH ₂ -		H	CH ₃ -
A1523	CH ₃ CH ₂ -		H	CH ₃ -
A1524	CH ₃ CH ₂ -		H	CH ₃ -
A1525	CH ₃ CH ₂ -		H	CH ₃ -
A1526	CH ₃ CH ₂ -		H	CH ₃ -
A1527	CH ₃ CH ₂ -		H	CH ₃ -
A1528	CH ₃ CH ₂ -		H	CH ₃ -
A1529	CH ₃ CH ₂ -		H	CH ₃ -
A1530	CH ₃ CH ₂ -		H	CH ₃ -
A1531	CH ₃ CH ₂ -		H	CH ₃ -
A1532	CH ₃ CH ₂ -		H	CH ₃ -
A1533	CH ₃ CH ₂ -		H	CH ₃ -

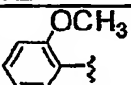
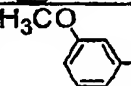
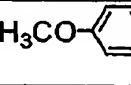
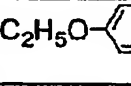
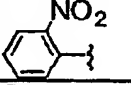
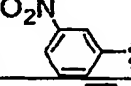
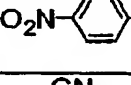
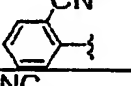
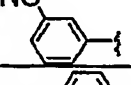
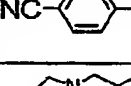
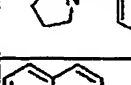
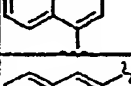
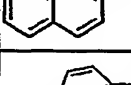
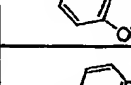
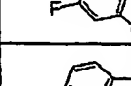
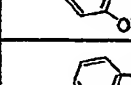
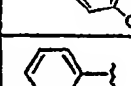
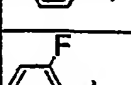

【0034】

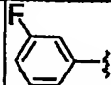

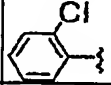
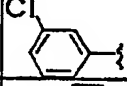
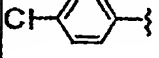
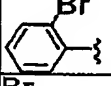
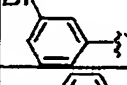
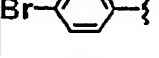
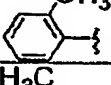
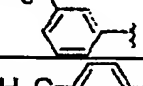

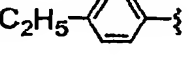
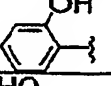
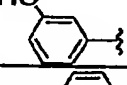
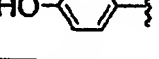
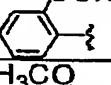
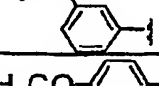
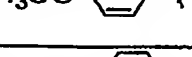
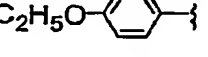
【表 2】

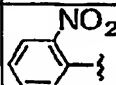
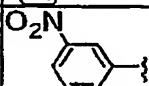
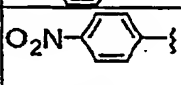
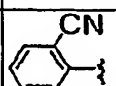
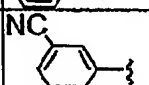
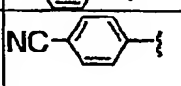
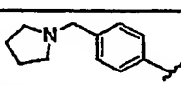
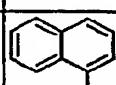
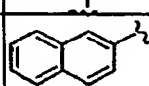
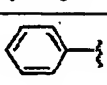
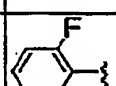
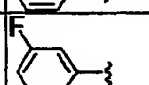
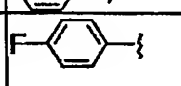
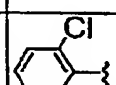
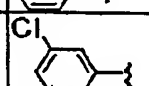
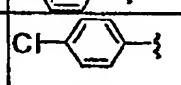
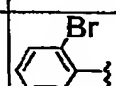
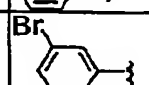
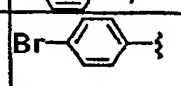
Table-2

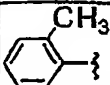
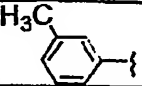
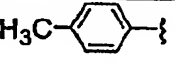
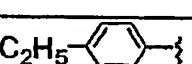
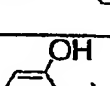
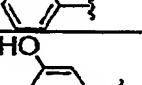

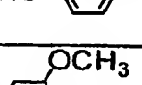
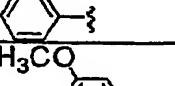
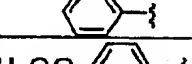

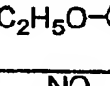
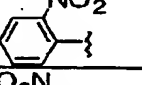
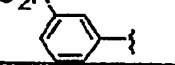
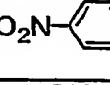
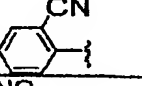
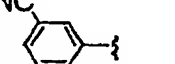
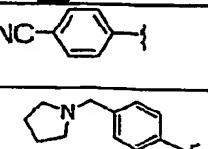
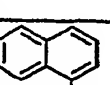
					
No.	R1	R2	R3	R4	R5
B1	CH3-	CH3-	H	H	H
B2	CH3-	CH3CH2-	H	H	H
B3	CH3-		H	H	H
B4	CH3-		H	H	H
B5	CH3-		H	H	H
B6	CH3-		H	H	H
B7	CH3-		H	H	H
B8	CH3-		H	H	H
B9	CH3-		H	H	H
B10	CH3-		H	H	H
B11	CH3-		H	H	H
B12	CH3-		H	H	H
B13	CH3-		H	H	H
B14	CH3-		H	H	H
B15	CH3-		H	H	H

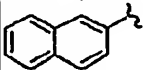



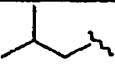


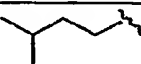




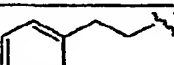




No.	R1	R2	R3	R4	R5
B16	CH ₃ -		H	H	H
B17	CH ₃ -		H	H	H
B18	CH ₃ -		H	H	H
B19	CH ₃ -		H	H	H
B20	CH ₃ -		H	H	H
B21	CH ₃ -		H	H	H
B22	CH ₃ -		H	H	H
B23	CH ₃ -		H	H	H
B24	CH ₃ -		H	H	H
B25	CH ₃ -		H	H	H
B26	CH ₃ -		H	H	H
B27	CH ₃ -		H	H	H
B28	CH ₃ -		H	H	H
B29	CH ₃ -		H	H	H
B30	CH ₃ -		H	H	H
B31	CH ₃ -		H	H	H
B32	CH ₃ -		H	H	H
B33	CH ₃ -		H	H	H
B34	CH ₃ -		H	H	H

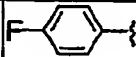
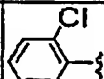
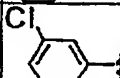
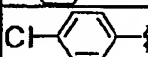
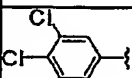
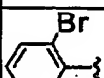
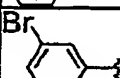
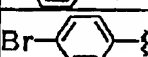
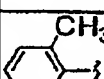
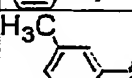

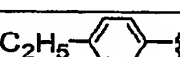
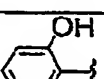
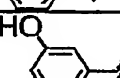
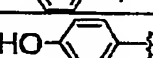
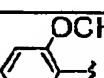
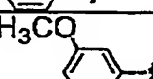
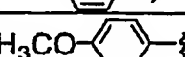
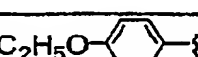
No.	R1	R2	R3	R4	R5
B35	CH ₃ -		H	H	H
B36	CH ₃ -		H	H	H
B37	CH ₃ -		H	H	H
B38	CH ₃ -		H	H	H
B39	CH ₃ -		H	H	H
B40	CH ₃ -		H	H	H
B41	CH ₃ -		H	H	H
B42	CH ₃ -		H	H	H
B43	CH ₃ -		H	H	H
B44	CH ₃ -		H	H	H
B45	CH ₃ -		H	H	H
B46	CH ₃ -		H	H	H
B47	CH ₃ -		H	H	H
B48	CH ₃ -		H	H	H
B49	CH ₃ -		H	H	H
B50	CH ₃ -		H	H	H
B51	CH ₃ -		H	H	H
B52	CH ₃ -		OH	H	H
B53	CH ₃ -		OH	H	H

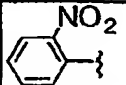
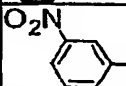
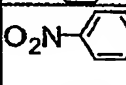
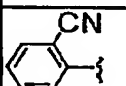
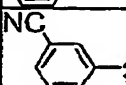
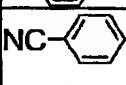
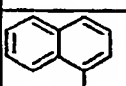
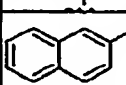
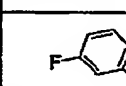
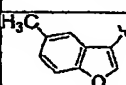
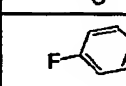
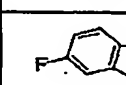
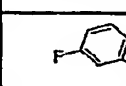
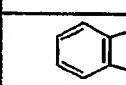
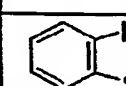
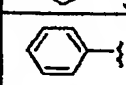
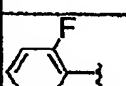
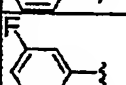
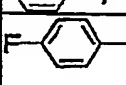
No.	R1	R2	R3	R4	R5
B54	CH ₃ -		OH	H	H
B55	CH ₃ -		OH	H	H
B56	CH ₃ -		OH	H	H
B57	CH ₃ -		OH	H	H
B58	CH ₃ -		OH	H	H
B59	CH ₃ -		OH	H	H
B60	CH ₃ -		OH	H	H
B61	CH ₃ -		OH	H	H
B62	CH ₃ -		OH	H	H
B63	CH ₃ -		OH	H	H
B64	CH ₃ -		OH	H	H
B65	CH ₃ -		OH	H	H
B66	CH ₃ -		OH	H	H
B67	CH ₃ -		OH	H	H
B68	CH ₃ -		OH	H	H
B69	CH ₃ -		OH	H	H
B70	CH ₃ -		OH	H	H
B71	CH ₃ -		OH	H	H
B72	CH ₃ -		OH	H	H

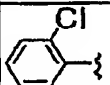
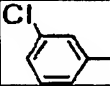
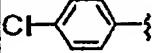
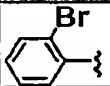
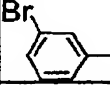
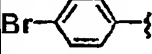
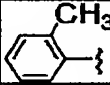
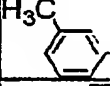
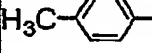
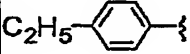
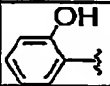
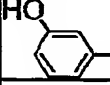
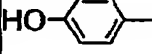
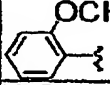
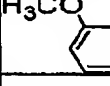
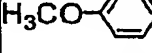
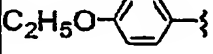
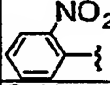
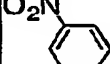
No.	R1	R2	R3	R4	R5
B73	CH3-		OH	H	H
B74	CH3-		OH	H	H
B75	CH3-		OH	H	H
B76	CH3-		OH	H	H
B77	CH3-		OH	H	H
B78	CH3-		OH	H	H
B79	CH3-		OH	H	H
B80	CH3-		OH	H	H
B81	CH3-		OH	H	H
B82	CH3-		CN	H	H
B83	CH3-		CN	H	H
B84	CH3-		CN	H	H
B85	CH3-		CN	H	H
B86	CH3-		CN	H	H
B87	CH3-		CN	H	H
B88	CH3-		CN	H	H
B89	CH3-		CN	H	H
B90	CH3-		CN	H	H
B91	CH3-		CN	H	H

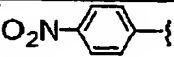
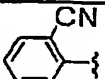
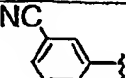
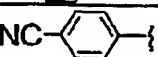
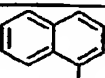
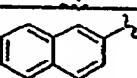
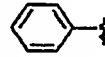
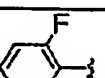
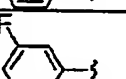
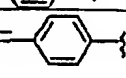
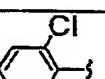
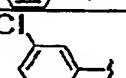
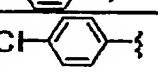
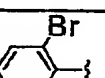
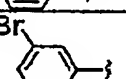
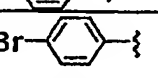
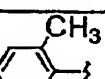
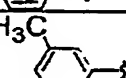
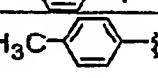
No.	R1	R2	R3	R4	R5
B92	CH ₃ -		CN	H	H
B93	CH ₃ -		CN	H	H
B94	CH ₃ -		CN	H	H
B95	CH ₃ -		CN	H	H
B96	CH ₃ -		CN	H	H
B97	CH ₃ -		CN	H	H
B98	CH ₃ -		CN	H	H
B99	CH ₃ -		CN	H	H
B100	CH ₃ -		CN	H	H
B101	CH ₃ -		CN	H	H
B102	CH ₃ -		CN	H	H
B103	CH ₃ -		CN	H	H
B104	CH ₃ -		CN	H	H
B105	CH ₃ -		CN	H	H
B106	CH ₃ -		CN	H	H
B107	CH ₃ -		CN	H	H
B108	CH ₃ -		CN	H	H
B109	CH ₃ -		CN	H	H
B110	CH ₃ -		CN	H	H

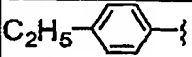
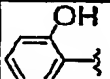
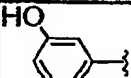

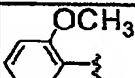
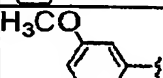
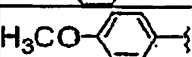
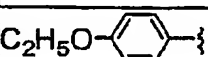
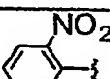
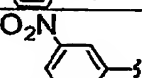

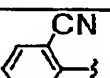
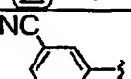
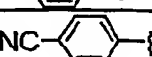
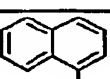
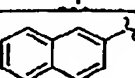
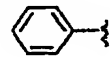

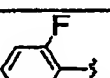

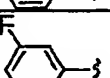

No.	R1	R2	R3	R4	R5
B111	CH3-		CN	H	H
B112	CH3-	H	H	CH3-	H
B113	CH3-	H	H	CH3CH2-	H
B114	CH3-	H	H		H
B115	CH3-	H	H		H
B116	CH3-	H	H		H
B117	CH3-	H	H		H
B118	CH3-	H	H		H
B119	CH3-	H	H		H
B120	CH3-	H	H		H
B121	CH3-	H	H		H
B122	CH3-	H	H		H
B123	CH3-	H	H		H
B124	CH3-	H	H		H
B125	CH3-	H	H		H
B126	CH3-	H	H		H
B127	CH3-	H	H		H
B128	CH3-	H	H		H
B129	CH3-	H	H		H



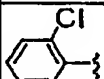

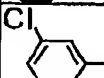

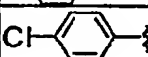

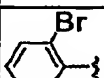

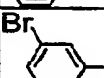

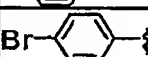

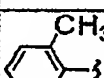

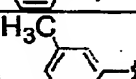

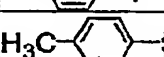

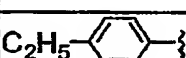

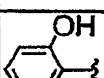

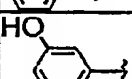

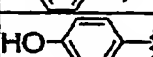

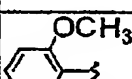

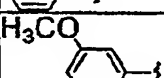



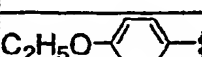



No.	R1	R2	R3	R4	R5
B130	CH ₃ -	H	H		H
B131	CH ₃ -	H	H		H
B132	CH ₃ -	H	H		H
B133	CH ₃ -	H	H		H
B134	CH ₃ -	H	H		H
B135	CH ₃ -	H	H		H
B136	CH ₃ -	H	H		H
B137	CH ₃ -	H	H		H
B138	CH ₃ -	H	H		H
B139	CH ₃ -	H	H		H
B140	CH ₃ -	H	H		H
B141	CH ₃ -	H	H		H
B142	CH ₃ -	H	H		H
B143	CH ₃ -	H	H		H
B144	CH ₃ -	H	H		H
B145	CH ₃ -	H	H		H
B146	CH ₃ -	H	H		H
B147	CH ₃ -	H	H		H
B148	CH ₃ -	H	H		H

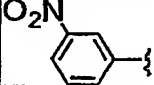

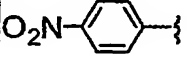

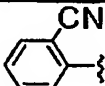

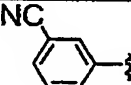

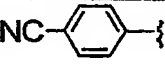

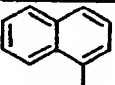

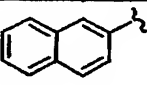

No.	R1	R2	R3	R4	R5
B149	CH ₃ -	H	H		H
B150	CH ₃ -	H	H		H
B151	CH ₃ -	H	H		H
B152	CH ₃ -	H	H		H
B153	CH ₃ -	H	H		H
B154	CH ₃ -	H	H		H
B155	CH ₃ -	H	H		H
B156	CH ₃ -	H	H		H
B157	CH ₃ -	H	H		H
B158	CH ₃ -	H	H		H
B159	CH ₃ -	H	H		H
B160	CH ₃ -	H	H		H
B161	CH ₃ -	H	H		H
B162	CH ₃ -	H	H		H
B163	CH ₃ -	H	H		H
B164	CH ₃ -	H	H		OH
B165	CH ₃ -	H	H		OH
B166	CH ₃ -	H	H		OH
B167	CH ₃ -	H	H		OH

No.	R1	R2	R3	R4	R5
B168	CH ₃ -	H	H		OH
B169	CH ₃ -	H	H		OH
B170	CH ₃ -	H	H		OH
B171	CH ₃ -	H	H		OH
B172	CH ₃ -	H	H		OH
B173	CH ₃ -	H	H		OH
B174	CH ₃ -	H	H		OH
B175	CH ₃ -	H	H		OH
B176	CH ₃ -	H	H		OH
B177	CH ₃ -	H	H		OH
B178	CH ₃ -	H	H		OH
B179	CH ₃ -	H	H		OH
B180	CH ₃ -	H	H		OH
B181	CH ₃ -	H	H		OH
B182	CH ₃ -	H	H		OH
B183	CH ₃ -	H	H		OH
B184	CH ₃ -	H	H		OH
B185	CH ₃ -	H	H		OH
B186	CH ₃ -	H	H		OH

No.	R1	R2	R3	R4	R5
B187	CH ₃ -	H	H		OH
B188	CH ₃ -	H	H		OH
B189	CH ₃ -	H	H		OH
B190	CH ₃ -	H	H		OH
B191	CH ₃ -	H	H		OH
B192	CH ₃ -	H	H		OH
B193	CH ₃ -	H	H		CN
B194	CH ₃ -	H	H		CN
B195	CH ₃ -	H	H		CN
B196	CH ₃ -	H	H		CN
B197	CH ₃ -	H	H		CN
B198	CH ₃ -	H	H		CN
B199	CH ₃ -	H	H		CN
B200	CH ₃ -	H	H		CN
B201	CH ₃ -	H	H		CN
B202	CH ₃ -	H	H		CN
B203	CH ₃ -	H	H		CN
B204	CH ₃ -	H	H		CN
B205	CH ₃ -	H	H		CN

No.	R1	R2	R3	R4	R5
B206	CH ₃ -	H	H		CN
B207	CH ₃ -	H	H		CN
B208	CH ₃ -	H	H		CN
B209	CH ₃ -	H	H		CN
B210	CH ₃ -	H	H		CN
B211	CH ₃ -	H	H		CN
B212	CH ₃ -	H	H		CN
B213	CH ₃ -	H	H		CN
B214	CH ₃ -	H	H		CN
B215	CH ₃ -	H	H		CN
B216	CH ₃ -	H	H		CN
B217	CH ₃ -	H	H		CN
B218	CH ₃ -	H	H		CN
B219	CH ₃ -	H	H		CN
B220	CH ₃ -	H	H		CN
B221	CH ₃ -	H	H		CN
B222	CH ₃ -	H	H		
B223	CH ₃ -	H	H		
B224	CH ₃ -	H	H		

No.	R1	R2	R3	R4	R5
B225	CH ₃ -	H	H		
B226	CH ₃ -	H	H		
B227	CH ₃ -	H	H		
B228	CH ₃ -	H	H		
B229	CH ₃ -	H	H		
B230	CH ₃ -	H	H		
B231	CH ₃ -	H	H		
B232	CH ₃ -	H	H		
B233	CH ₃ -	H	H		
B234	CH ₃ -	H	H		
B235	CH ₃ -	H	H		
B236	CH ₃ -	H	H		
B237	CH ₃ -	H	H		
B238	CH ₃ -	H	H		
B239	CH ₃ -	H	H		
B240	CH ₃ -	H	H		
B241	CH ₃ -	H	H		
B242	CH ₃ -	H	H		
B243	CH ₃ -	H	H		

No.	R1	R2	R3	R4	R5
B244	CH ₃ -	H	H		
B245	CH ₃ -	H	H		
B246	CH ₃ -	H	H		
B247	CH ₃ -	H	H		
B248	CH ₃ -	H	H		
B249	CH ₃ -	H	H		
B250	CH ₃ -	H	H		

【0035】

式 (I) で表わされる本発明の化合物の特に好適な例として、

2- (3-フェニルピペラジン-1-イル) -3-メチル-6- (4-ピリミジル) -3H-ピリミジン-4-オン；

2- (3- (4-フルオロフェニル) ピペラジン-1-イル) -3-メチル-6- (4-ピリミジル) -3H-ピリミジン-4-オン；

2- (3- (3-フルオロフェニル) ピペラジン-1-イル) -3-メチル-6- (4-ピリミジル) -3H-ピリミジン-4-オン；

2- (3- (2-フルオロフェニル) ピペラジン-1-イル) -3-メチル-6- (4-ピリミジル) -3H-ピリミジン-4-オン；

2- (3- (4-クロロフェニル) ピペラジン-1-イル) -3-メチル-6- (4-ピリミジル) -3H-ピリミジン-4-オン；

2- (3- (3-クロロフェニル) ピペラジン-1-イル) -3-メチル-6- (4-ピリミジル) -3H-ピリミジン-4-オン；

2- (3- (2-クロロフェニル) ピペラジン-1-イル) -3-メチル-6- (4-ピリミジル) -3H-ピリミジン-4-オン；

2- (3- (4-ブロモフェニル) ピペラジン-1-イル) -3-メチル-6-

- (4-ピリミジル) - 3H-ピリミジン-4-オン;
- 2-(3-(3-ブロモフェニル) ピペラジン-1-イル) - 3-メチル-6-(4-ピリミジル) - 3H-ピリミジン-4-オン;
- 2-(3-(2-ブロモフェニル) ピペラジン-1-イル) - 3-メチル-6-(4-ピリミジル) - 3H-ピリミジン-4-オン;
- 2-(3-(4-シアノフェニル) ピペラジン-1-イル) - 3-メチル-6-(4-ピリミジル) - 3H-ピリミジン-4-オン;
- 2-(3-(3-シアノフェニル) ピペラジン-1-イル) - 3-メチル-6-(4-ピリミジル) - 3H-ピリミジン-4-オン;
- 2-(3-(2-シアノフェニル) ピペラジン-1-イル) - 3-メチル-6-(4-ピリミジル) - 3H-ピリミジン-4-オン;
- 2-(3-(4-メトキシフェニル) ピペラジン-1-イル) - 3-メチル-6-(4-ピリミジル) - 3H-ピリミジン-4-オン;
- 2-(3-(3-メトキシフェニル) ピペラジン-1-イル) - 3-メチル-6-(4-ピリミジル) - 3H-ピリミジン-4-オン;
- 2-(3-(2-メトキシフェニル) ピペラジン-1-イル) - 3-メチル-6-(4-ピリミジル) - 3H-ピリミジン-4-オン;
- 2-(3-(2-エトキシフェニル) ピペラジン-1-イル) - 3-メチル-6-(4-ピリミジル) - 3H-ピリミジン-4-オン;
- 2-(3-(6-フルオロ-2-メトキシフェニル) ピペラジン-1-イル) - 3-メチル-6-(4-ピリミジル) - 3H-ピリミジン-4-オン;
- 2-(3-(5-フルオロ-2-メトキシフェニル) ピペラジン-1-イル) - 3-メチル-6-(4-ピリミジル) - 3H-ピリミジン-4-オン;
- 2-(3-(4-フルオロ-2-メトキシフェニル) ピペラジン-1-イル) - 3-メチル-6-(4-ピリミジル) - 3H-ピリミジン-4-オン;
- (S) - 2-(3-(4-フルオロ-2-メトキシフェニル) ピペラジン-1-イル) - 3-メチル-6-(4-ピリミジル) - 3H-ピリミジン-4-オン;
- (R) - 2-(3-(4-フルオロ-2-メトキシフェニル) ピペラジン-1-イル) - 3-メチル-6-(4-ピリミジル) - 3H-ピリミジン-4-オン;

- 2- (3- (4-クロロ-2-メトキシフェニル) ピペラジン-1-イル) -3-メチル-6- (4-ピリミジル) -3H-ピリミジン-4-オン;
- 2- (3- (5-ブromo-2-メトキシフェニル) ピペラジン-1-イル) -3-メチル-6- (4-ピリミジル) -3H-ピリミジン-4-オン;
- 2- (3- (2, 6-ジクロロフェニル) ピペラジン-1-イル) -3-メチル-6- (4-ピリミジル) -3H-ピリミジン-4-オン;
- 2- (3- (2, 4-ジメトキシフェニル) ピペラジン-1-イル) -3-メチル-6- (4-ピリミジル) -3H-ピリミジン-4-オン;
- 2- (3- (3, 4-ジメトキシフェニル) ピペラジン-1-イル) -3-メチル-6- (4-ピリミジル) -3H-ピリミジン-4-オン;
- 2- (3- (2, 5-ジメトキシフェニル) ピペラジン-1-イル) -3-メチル-6- (4-ピリミジル) -3H-ピリミジン-4-オン;
- 2- (3- (2, 6-ジメトキシフェニル) ピペラジン-1-イル) -3-メチル-6- (4-ピリミジル) -3H-ピリミジン-4-オン;
- 2- (3- (2, 4-ジフルオロ-6-メトキシフェニル) ピペラジン-1-イル) -3-メチル-6- (4-ピリミジル) -3H-ピリミジン-4-オン;
- 2- (3- (1-ナフチル) ピペラジン-1-イル) -3-メチル-6- (4-ピリミジル) -3H-ピリミジン-4-オン;
- 2- (3- (2-ナフチル) ピペラジン-1-イル) -3-メチル-6- (4-ピリミジル) -3H-ピリミジン-4-オン;
- 2- (3- (2, 3-ジヒドロベンゾフラン-7-イル) ピペラジン-1-イル) -3-メチル-6- (4-ピリミジル) -3H-ピリミジン-4-オン;
- 2- (3- (ベンゾフラン-2-イル) ピペラジン-1-イル) -3-メチル-6- (4-ピリミジル) -3H-ピリミジン-4-オン;
- 2- (3- (4- (ピロリジン-1-イル-メチル) フェニル) ピペラジン-1-イル) -3-メチル-6- (4-ピリミジル) -3H-ピリミジン-4-オン;
- 2- (3- (4- (ピロリジン-1-イル) フェニル) ピペラジン-1-イル) -3-メチル-6- (4-ピリミジル) -3H-ピリミジン-4-オン;

2-(3-(2-メトキシ-4-(ピロリジン-1-イル)フェニル)ピペラジン-1-イル)-3-メチル-6-(4-ピリミジル)-3H-ピリミジン-4-オン;

2-(3-(2-メトキシ-5-(ピロリジン-1-イル)フェニル)ピペラジン-1-イル)-3-メチル-6-(4-ピリミジル)-3H-ピリミジン-4-オン;

2-(3-(4-(フェニル)フェニル)ピペラジン-1-イル)-3-メチル-6-(4-ピリミジル)-3H-ピリミジン-4-オン;

2-(3-(4-(4-フルオロフェニル)フェニル)ピペラジン-1-イル)-3-メチル-6-(4-ピリミジル)-3H-ピリミジン-4-オン;

2-(3-(4-(4-メトキシフェニル)フェニル)ピペラジン-1-イル)-3-メチル-6-(4-ピリミジル)-3H-ピリミジン-4-オン;

2-(3-(4-(2-メトキシフェニル)フェニル)ピペラジン-1-イル)-3-メチル-6-(4-ピリミジル)-3H-ピリミジン-4-オン;

2-(3-(4-(モルホリン-4-イル)フェニル)ピペラジン-1-イル)-3-メチル-6-(4-ピリミジル)-3H-ピリミジン-4-オン;

2-(3-(4-(4-メチルピペラジン-1-イル)フェニル)ピペラジン-1-イル)-3-メチル-6-(4-ピリミジル)-3H-ピリミジン-4-オン;

2-(3-(4-フルオロ-2-メトキシフェニル)-4-メチルピペラジン-1-イル)-3-メチル-6-(4-ピリミジル)-3H-ピリミジン-4-オン;

(S)-2-(3-(4-フルオロ-2-メトキシフェニル)-4-メチルピペラジン-1-イル)-3-メチル-6-(4-ピリミジル)-3H-ピリミジン-4-オン;

(R)-2-(3-(4-フルオロ-2-メトキシフェニル)-4-メチルピペラジン-1-イル)-3-メチル-6-(4-ピリミジル)-3H-ピリミジン-4-オン;

2-(4-アセチル-3-(4-フルオロ-2-メトキシフェニル)ピペラジン

—1—イル)—3—メチル—6—(4—ピリミジル)—3H—ピリミジン—4—オン;

2—(4—ベンジル—3—(4—フルオロ—2—メトキシフェニル) ピペラジン—1—イル)—3—メチル—6—(4—ピリミジル)—3H—ピリミジン—4—オン;

2—(4—(4—フルオロフェニル) ピペリジン—1—イル)—3—メチル—6—(4—ピリミジル)—3H—ピリミジン—4—オン;

2—(4—シアノ—4—フェニルピペリジン—1—イル)—3—メチル—6—(4—ピリミジル)—3H—ピリミジン—4—オン;

2—(4—(6—フルオロベンゾフラン—3—イル) ピペリジン—1—イル)—3—メチル—6—(4—ピリミジル)—3H—ピリミジン—4—オン;

2—(3—(ベンゾイソキサゾール—3—イル) ピペリジン—1—イル)—3—メチル—6—(4—ピリミジル)—3H—ピリミジン—4—オン;

(S)—2—(3—(ベンゾイソキサゾール—3—イル) ピペリジン—1—イル)—3—メチル—6—(4—ピリミジル)—3H—ピリミジン—4—オン;

(R)—2—(3—(ベンゾイソキサゾール—3—イル) ピペリジン—1—イル)—3—メチル—6—(4—ピリミジル)—3H—ピリミジン—4—オン;

2—(3—(6—フルオロベンゾイソキサゾール—3—イル) ピペリジン—1—イル)—3—メチル—6—(4—ピリミジル)—3H—ピリミジン—4—オン;

2—(4—(6—フルオロベンゾイソキサゾール—3—イル) ピペリジン—1—イル)—3—メチル—6—(4—ピリミジル)—3H—ピリミジン—4—オン;

2—(4—(5—メチルベンゾフラン—3—イル) ピペリジン—1—イル)—3—メチル—6—(4—ピリミジル)—3H—ピリミジン—4—オン; および

2—(4—(6—フルオロベンゾチオフェン—3—イル) ピペリジン—1—イル)—3—メチル—6—(4—ピリミジル)—3H—ピリミジン—4—オンが挙げ

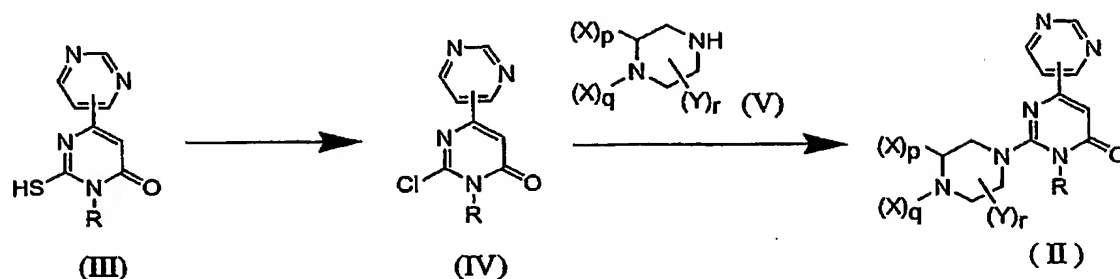
られる。上記の好ましい化合物の塩、又は上記の化合物又はその塩の溶媒和物若しくは水和物もまた好ましい。

【0036】

前記式(I)で表される3—置換—4—ピリミドン化合物は、例えば、下記に

説明する方法に従って製造することができる。

【化 8】



(上記スキームにおいて、R、X、及びYの定義は上記と同義である。)

【0037】

上記式 (I I I) で表される 2-チオピリミドン誘導体は、EP 354, 179 に記載の方法に修正を加えたものによって容易に製造される。反応は、水酸化ナトリウム、水酸化カリウム、ナトリウムメトキシド、ナトリウムエトキシド、カリウム *tert*-ブトキシド、炭酸ナトリウム、炭酸水素ナトリウム、炭酸カリウム、トリエチルアミン、ジイソプロピルエチルアミン、1, 8-ジアザビシクロ [5, 4, 0] ウンデセ-7-エンなどの塩基の存在下、窒素又はアルゴン雰囲気下又は通常の空气中、0℃～200℃の範囲の好適な温度で、1～100時間で行えばよく、目的化合物 (I I I) を得る。反応の溶媒の例としては、例えば、メタノール、エタノール、1-プロパノール、イソプロパノール、*tert*-ブタノール、エチレングリコール、プロピレングリコール等のアルコール性溶媒；ジエチルエーテル、*tert*-ブチルメチルエーテル、テトラヒドロフラン、イソプロピルエーテル等のエーテル系溶媒；ベンゼン、トルエン、キシレン等の炭化水素系溶媒；ジクロロメタン、クロロホルム、ジクロロエタン等のハロゲン化炭化水素系溶媒；ホルムアミド、N, N-ジメチルホルムアミド、N, N-ジメチルアセトアミド、N-メチルピロリドン、ジメチルスルホキシド、スルホラン、ヘキサメチルホスホリクトリアミド等の非プロトン性極性溶媒、水などが挙げられる。通常は、用いる塩基に適した単独の溶媒もしくは2種類以上の溶媒の混合物を使用すればよい。

【0038】

続いて、2-チオピリミドン誘導体 (I I I) は塩素化試薬により2-クロロ

ピリミドン (I V) に変換する。反応時間と温度は用いる塩素化試薬による。この反応の塩素化試薬の例としては塩化チオニル、塩化チオニルとジメチルホルムアミド、塩化ホスホリル、塩化ホスホリルとジメチルホルムアミド、塩化オキサリル、塩化ホスホリルとジメチルホルムアミド、及び五塩化リンが挙げられる。

【0039】

上記式 (V) で示されるアミンは日本特許公開昭 52-139085 (1977) に示された方法に修正を加えたものにより、又は当業者に周知の方法に従って製造することができる。

【0040】

その後、塩化物誘導体 (I V) は、アミン (V) またはその塩と、水酸化ナトリウム、水酸化カリウム、ナトリウムメトキシド、ナトリウムエトキシド、炭酸ナトリウム、炭酸水素ナトリウム、炭酸カリウム、トリエチルアミン、ジイソプロピルエチルアミン、1, 8-ジアザビシクロ [5, 4, 0] ウンデセ-7-7-エンなどの塩基の存在下、窒素又はアルゴン雰囲気下又は通常の空气中、0℃～200℃の範囲の好適な温度で、0.1～100時間、反応させ、目的化合物 (I I) を得る。

【0041】

反応の溶媒の例としては、例えば、メタノール、エタノール、1-プロパノール、イソプロパノール、tert-ブタノール、エチレングリコール、プロピレングリコール等のアルコール性溶媒；ジエチルエーテル、tert-ブチルメチルエーテル、テトラヒドロフラン、イソプロピルエーテル等のエーテル系溶媒；ベンゼン、トルエン、キシレン等の炭化水素系溶媒；ジクロロメタン、クロロホルム、ジクロロエタン等のハロゲン化炭化水素系溶媒；ホルムアミド、N, N-ジメチルホルムアミド、N, N-ジメチルアセトアミド、N-メチルピロリドン、ジメチルスルホキシド、スルホラン、ヘキサメチルホスホリクトリアミド等の非プロトン性極性溶媒、水などが挙げられる。通常は、用いる塩基に適した単独の溶媒もしくは2種類以上の溶媒の混合物を使用すればよい。

【0042】

本発明の化合物はTPK1に対する阻害活性を有しており、アルツハイマー病

などの神経変性疾患においてTPK1活性を阻害することにより、 $A\beta$ の神経毒性及びPHFの形成を抑え、神経細胞死を阻止する。従って、本発明の化合物は、アルツハイマー病の予防及び／又は治療を根本的に可能にする医薬の有効成分として有用である。また、本発明の化合物は、虚血性脳血管障害、ダウン症候群、孤発性脳アミロイドアンギオパチーによる脳出血、進行性核上麻痺、亜急性硬化性全脳脳炎、脳炎後パーキンソン症候群、拳闘家脳症、グアム・パーキンソン痴呆複合症、レビー小体病、ピック病、皮質底部変性、前頭側頭性痴呆、血管性痴呆、急性発作及び外傷性損傷、脳及び脊髄損傷、末梢性ニューロパシー、網膜症、及び緑内障などの神経変性疾患；インスリン非依存性糖尿病（2型糖尿病など）、肥満症、躁鬱病、精神分裂病、脱毛症、及び、乳癌、非小細胞肺癌、甲状腺癌、T又はB細胞白血病、ウイルス誘導性腫瘍などの癌の予防及び／又は治療のための医薬の有効成分として有用である。

【0043】

本発明の医薬の有効成分としては、前記式（I）で表される化合物及び生理学的に許容されるその塩、並びにそれらの溶媒和物及びそれらの水和物からなる群より選ばれる物質を用いることができる。本発明の医薬としては、該物質自体を投与してもよいが、有効成分として前記の物質と1又は2以上の製剤用添加物を含む医薬組成物の形態の医薬を投与することが望ましい。本発明の医薬の有効成分としては、上記の物質の2種以上を組み合わせ用いてもよい。上記医薬組成物には、例えば、アルツハイマー病、血管性痴呆、急性発作及び外傷性損傷、脳及び脊髄損傷、末梢性ニューロパシー、網膜症、及び緑内障などの神経変性疾患；インスリン非依存性糖尿病（2型糖尿病など）、肥満症、躁鬱病、精神分裂病、脱毛症、及び、乳癌、非小細胞肺癌、甲状腺癌、T又はB細胞白血病、ウイルス誘導性腫瘍などの癌の治療のための他の医薬の有効成分を配合することも可能である。

【0044】

医薬組成物の種類は特に限定されず、経口又は非経口投与用の任意の製剤形態として提供される。例えば、医薬組成物は、顆粒剤、細粒剤、散剤、硬カプセル剤、軟カプセル剤、シロップ剤、乳剤、懸濁剤、液剤等の経口投与用医薬組成物

の形態として、又は、静脈内投与用、筋肉内投与用、若しくは皮下投与用の注射剤、点滴剤、経皮吸収剤、経粘膜吸収剤、点鼻剤、吸入剤、坐剤等の非経口投与用医薬組成物の形態として調製することができる。注射剤や点滴剤は、凍結乾燥形態などの粉末状の製剤として調製し、使用直前に生理食塩水などの適宜の水性媒体に溶解して用いることもできる。また、高分子で被覆したものなどの徐放製剤を脳内に直接投与することも可能である。

【0045】

医薬組成物の製造に用いられる製剤用添加物の種類、有効成分に対する製剤用添加物の含量比、及び医薬組成物の製造方法は、当業者が適宜選択することが可能である。製剤用添加物としては無機又は有機物質、あるいは固体又は液体の物質を用いることができる。一般的には、製剤用添加物は有効成分質量に対して1質量%から90質量%の範囲の割合で配合することができる。

【0046】

固体の医薬組成物の製造に用いられる賦形剤の例としては、例えば、乳糖、蔗糖、デンプン、タルク、セルロース、デキストリン、カオリン、炭酸カルシウム等が挙げられる。経口投与のための液体組成物の製造には、一般的に用いられる不活性な希釈剤、例えば水又は植物油等を用いることができる。この液体組成物には、不活性な希釈剤以外に、補助剤、例えば湿潤剤、懸濁補助剤、甘味剤、芳香剤、着色剤又は保存剤等を配合してもよい。液体組成物をゼラチンのような吸収されうる物質のカプセル中に充填してもよい。非経口投与用の組成物、例えば注射剤や坐剤の製造に用いられる溶剤又は懸濁剤の例としては、水、プロピレングリコール、ポリエチレングリコール、ベンジルアルコール、オレイン酸エチル、レシチン等が挙げられる。坐剤に用いられる基剤の例としては、例えばカカオ脂、乳化カカオ脂、ラウリン脂、ウィテップゾールが挙げられる。

【0047】

本発明の医薬の投与量及び投与回数は特に限定されず、予防及び／又は治療の目的、疾患の種類、患者の体重や年齢、疾患の重篤度などの条件に応じて、適宜選択することが可能である。一般的には、経口投与における成人一日あたりの投与量は0.01～1000mg（有効成分質量）程度であり、一日1回又は数回

に分けて、あるいは数日ごとに投与することができる。該医薬を注射剤として用いる場合には、成人に対して一日量 0.001～100mg（有効成分質量）を連続投与又は間欠投与することが望ましい。

【0048】

【実施例】

本発明を実施例によりさらに具体的に説明するが、本発明の範囲は下記の実施例に限定されることはない。実施例中の化合物番号は、上記の表中の化合物番号に対応している。

【0049】

参考例 1：2-メルカプト-3-メチル-6-(4-ピリミジル)-3H-ピリミジン-4-オンの合成

エチル-3-オキソ-3-(4-ピリジル)プロピオン酸（34.1g, 176mmol）、N-メチルチオ尿素（47.5g, 527mmol）、及び 1,8-ジアザビシクロ[5,4,0]7-ウンデセン（26.3ml, 176mmol）のエタノール（340ml）溶液は、2時間還流し、氷水で冷却した後、メタンスルホン酸（16.9g, 176mmol）の水（70ml）溶液を加えた。析出物を水で洗い、濾過、乾燥して標記化合物（30.2g, 78%）を得た。

$^1\text{H-NMR}$ (DMSO- d_6) δ : 3.56 (s, 3H), 6.88 (s, 1H), 8.24 (dd, $J=1.2, 5.4\text{ Hz}$, 2H), 9.05 (dd, $J=5.4\text{ Hz}$, 1H), 11.94 (s, 1H).

【0050】

参考例 2：2-クロロ-3-メチル-6-(4-ピリミジル)-3H-ピリミジン-4-オンの合成

塩化ホスホリル（4.60g, 30mmol）をジメチルホルミアミド（32ml）に加え、0℃で20分間攪拌した。2-メルカプト-3-メチル-6-(4-ピリミジル)-3H-ピリミジン-4-オン（4.40g, 20mmol）をこの溶液に加え、5分間攪拌し、その後、70℃で2時間攪拌した。反応液を氷水に注ぎ、固体炭酸カリウムで中和し、酢酸エチルで抽出した。有機層を食塩

水で洗い、硫酸ナトリウムで乾燥し、減圧留去した。残渣をシリカゲルカラムクロマトグラフィー（酢酸エチル）で精製し、標記化合物（1.20 g, 27%）を得た。

$^1\text{H-NMR}$ (CDCl_3) δ : 3.74 (s, 3H), 7.56 (s, 1H), 8.18 (d, $J=5.1\text{ Hz}$, 1H), 8.92 (d, $J=5.1\text{ Hz}$, 1H), 9.30 (s, 1H).

MS $[\text{M}+\text{H}]^+$: 223.

【0051】

実施例 1: 2-(2-(4-フルオロ-2-メトキシフェニル)ピペラジン-4-イル)-3-メチル-6-(4-ピリミジル)-ピリミジン-4-オンの合成
2-ブロモ-5-フルオロアニソール (11.8 g, 57.6 mmol) のテトラヒドロフラン (60 ml) 溶液を少量の 1, 2-ジブロモエタンを含む還流テトラヒドロフラン (32 ml) 中のマグネシウム (1.40 g, 57.6 mmol) に滴下し、15 分還流した。テトラヒドロフラン (50 ml) を添加後、この溶液を -78°C に冷却し、ジエチルエーテル (50 ml) 中のシュウ酸ジエチル (7.41 g, 50.7 mmol) を滴下した。30 分間、同じ温度で攪拌した後、この溶液を -10°C に温め、1 N 塩酸 (50 ml) 及び水を加えた。有機層をジエチルエーテルで抽出し、食塩水で洗って硫酸マグネシウムで乾燥した。減圧下で溶媒除去後、残渣をシリカゲルカラムクロマトグラフィー（溶出液: ヘキサン/酢酸エチル = 5/2）で精製し、2-(4-フルオロ-2-メトキシフェニル)-2-オキシ酢酸エチル (6.80 g, 59%) を得た。

$^1\text{H-NMR}$ (CDCl_3) δ : 1.40 (3H, t, $J=7.1\text{ Hz}$), 3.87 (3H, s), 4.89 (2H, q, $J=7.1\text{ Hz}$), 6.68 (1H, d, $J=10.5\text{ Hz}$), 6.77-6.81 (1H, m), 7.91-7.95 (1H, m)

【0052】

エチレンジアミン (0.60 g, 10.0 mmol) を 2-(4-フルオロ-2-メトキシフェニル)-2-オキシ酢酸エチル (2.26 g, 10.0 mmol) のエタノール (30 ml) 溶液に加え、4 時間還流した。減圧下で溶媒除去

後、残渣をエタノール-ジエチルエーテルで洗い、5, 6-ジヒドロ-3-(4-フルオロ-2-メトキシフェニル)ピラジノン (1.76 g, 79%) を得た。

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$^1\text{H-NMR}$ (CDCl_3) δ : 3.50-3.56 (2H, m), 3.81 (3H, s), 3.88-3.92 (2H, m), 6.65 (1H, d, $J=11.0\text{ Hz}$), 6.70-6.76 (1H, m), 6.89 (1H, bs), 7.36-7.40 (1H, m)

【0053】

5, 6-ジヒドロ-3-(4-フルオロ-2-メトキシフェニル)ピラジノンを水素化リチウムアルミニウム (0.46 g, 12 mmol) のジエチルエーテル (25 ml) 溶液に加え、6時間還流した。水 (0.48 ml), 15%水酸化ナトリウム溶液 (0.48 ml)、そして再び水 (1.21 ml) を氷冷した溶液に加え、析出物を濾過しジクロロメタンで洗浄した。有機層は合わせて溶媒を留去し、2-(4-フルオロ-2-メトキシフェニル)ピペラジン (0.83 g, 99%) を得た。

$^1\text{H-NMR}$ (CDCl_3) δ : 2.02 (2H, s), 2.57-2.63 (1H, m), 2.80-2.89 (1H, m), 2.92-2.99 (2H, m), 3.06-3.12 (2H, m), 3.80 (3H, s), 4.06 (1H, d, $J=10.0\text{ Hz}$), 6.56-6.65 (2H, m), 7.40 (1H, t, $J=7.8\text{ Hz}$)

【0054】

2-クロロ-3-メチル-6-(4-ピリミジル)-ピリミジン-4-オン (223 mg, 1.0 mmol) を、2-(4-フルオロ-2-メトキシフェニル)ピペラジン、トリエチルアミン (0.15 ml, 1.1 mmol) の氷冷した N, N-ジメチルホルムアミド (10 ml) 溶液に加え、その温度で0.5時間攪拌し、その後、室温で3時間攪拌した。反応を氷水でクエンチし、析出物を水で洗い、乾燥して2-(2-(4-フルオロ-2-メトキシフェニル)ピペラジン-4-イル)-3-メチル-6-(4-ピリミジル)-ピリミジン-4-オン (262 mg, 66%) を得た。

$^1\text{H-NMR}$ (CDCl_3) δ : 2.89–2.98 (1H, m), 3.22–3.31 (3H, m), 3.60 (3H, s), 3.62–3.71 (2H, m), 3.86 (3H, s), 4.39–4.44 (1H, m), 6.43–6.73 (2H, m), 7.33 (1H, s), 7.52–7.56 (1H, m), 8.19 (1H, d, $J=5.1\text{ Hz}$), 8.87 (1H, d, $J=5.2\text{ Hz}$), 9.28 (1H, d, $J=1.2\text{ Hz}$).

1, 4-ジオキサン (0.2 ml) 中の 4N 塩酸を、ジクロロメタン (5 ml) 中の 2-(2-(4-フルオロ-2-メトキシフェニル) ピペラジン-4-イル)-3-メチル-6-(4-ピリミジル)-ピリミジン-4-オン (238 mg, 0.6 mmol) に加え 15 分攪拌した。溶媒を除いた後、メタノールと酢酸エチルで洗い、乾燥して、標記化合物を得た。(223 mg, 86%)

【0055】

実施例 2: 2-(2-(4-クロロフェニル) ピペラジン-4-イル)-3-メチル-6-(4-ピリミジル) ピリミジン-4-オンの合成

4-クロロフェナシルブロミド (11.11 g, 65.9 mmol) と水 (1.7 ml) のジメチルスルホキシド (60 ml) 溶液を攪拌した。水を加え、溶液を酢酸エチルで 3 回抽出し、水で 2 回そして食塩水で洗浄、その後、硫酸ナトリウムで乾燥した。溶媒を除去後、残渣をヘキサン-酢酸エチルで洗い、乾燥して、4-クロロフェニルグリオキサール (4.43 g, 50%) を得た。

$^1\text{H-NMR}$ (CDCl_3) δ : 4.02–4.16 (2H, m), 5.90–5.95 (1H, m), 7.45–7.53 (2H, m), 8.05–8.11 (2H, m).

エチレンジアミン (1.90 g, 31.6 mmol) のメタノール (10 ml) 溶液を氷冷した 4-クロロフェニルグリオキサール (4.43 g, 26.3 mmol) のメタノール (100 ml) とテトラヒドロフラン (30 ml) 溶液に加え、10 分間攪拌した。テトラヒドロホウ酸ナトリウム (3.26 g, 86.3 mmol) を加えた後、さらにメタノール (50 ml) を加え一晩攪拌した。溶媒を除去後、希釈塩酸を加え、エーテルで 2 回抽出した。水酸化ナトリウムを加えた後、塩基性水層をジクロロメタンで 3 回抽出し、食塩水で洗浄、その後、

硫酸ナトリウムで乾燥した。ろ過で溶媒を除去した後、残渣をシリカゲルカラムクロマトグラフィー（溶出液：ジクロロメタン／エタノール＝10／1からジクロロメタン／エタノール／ジエチルアミン＝20／2／1）で精製し、2-（4-クロロフェニル）-ピペラジン（0.43 g, 9%）を得た。

$^1\text{H-NMR}$ (CDCl_3) δ : 2.67 (1H, dd, $J=10.5, 12.0$ Hz), 2.87-3.03 (4H, m), 3.07-3.13 (1H, m), 3.77 (1H, dd, $J=2.7, 10.2$ Hz), 7.27-7.36 (4H, m)

【0056】

トリエチルアミン（528 mg, 5.2 mmol）を、2-（4-クロロフェニル）-ピペラジン（216 mg, 1.1 mmol）と2-クロロ-3-メチル-6-（4-ピリミジル）ピリミジン-4-オンの溶液に加え、50℃で2時間攪拌した。溶媒を減圧下で除いて、残渣に1N水酸化ナトリウム水溶液を加え、ジクロロメタンで抽出した。食塩水で洗浄、硫酸ナトリウムで乾燥した後、溶媒を減圧下で除去し、残渣をISOLUTE（登録商標）SI（International Solvent Technology, UK）（溶出液：ジクロロメタン／エタノール＝10／1）を用いて精製し、標記化合物（396 mg, 95%）を得た。

下記表中の化合物を上記の方法と同様にして調製した。下記表中の化合物番号は、前記の好ましい化合物の表に示された番号に対応する。

【0057】

【表 3】

Table 3

No.	NMR	MS[M+1]
A0262	(DMSO-d ₆): 3.47(3H, s), 3.48-3.66(4H, m), 3.89-4.02(2H, m), 4.98(1H, m), 7.06(1H, s), 7.35-7.59(3H, m), 7.99(1H, dd, J=7.2, 6.9Hz), 8.25(1H, dd, J=5.4, 1.2Hz), 9.01(1H, d, J=5.1Hz), 9.31(1H, s), 9.84(1H, m), 10.19(1H, m).	367
A0263	(CDCl ₃): 3.01(1H, dd, J=10.5, 12.4Hz), 3.10-3.35(3H, m), 3.57(3H, s), 3.55-3.65(2H, m), 4.05(1H, dd, J=2.4, 10.4Hz), 7.00-7.10(1H, m), 7.30(1H, s), 7.22(2H, m), 7.30-7.42(2H, m), 8.15(1H, dd, J=1.3, 5.2Hz), 8.86(1H, d, J=5.2Hz), 9.27(1H, d, J=1.0Hz).	367
A0264	2.83(1H, dd, J=11.0, 11.9 Hz), 2.93(1H, s), 2.99-3.10(3H, m), 3.45(3H, s), 3.61-3.69(2H, m), 3.95(1H, dd, J=2.1, 10.3 Hz), 6.97(1H, s), 7.19(2H, t, J=8.8 Hz), 7.48-7.56(2H, m), 8.17(1H, dd, J=1.0, 5.0 Hz), 8.99(1H, d, J=5.1 Hz), 9.29(1H, d, J=1.0 Hz)(DMSO-d ₆)	367

A0264(HCl)	3.39-3.47(2H, m), 3.45(3H, s), 3.55-3.66(2H, m), 3.86-3.96(2H, m), 4.64-4.71(1H, m), 7.05(1H, s), 7.36(2H, t, J=8.7 Hz), 7.77-7.81(2H, m), 8.23(1H, dd, J=1.2, 5.1 Hz), 9.02(1H, d, J=5.1 Hz), 9.32(1H, d, J=1.2 Hz), 9.79(1H, d, J=10.2 Hz), 10.13-10.28(1H, m)(DMSO-d6)	367
A0267	(CDCl ₃): 2.81(1H, dd, J=10.5, 12.6 Hz), 3.15-3.40(3H, m), 3.50-3.65(4H, m), 3.65-3.80(1H, m), 4.51(1H, dd, J=2.7, 10.5 Hz), 7.20-7.45(4H, m), 7.74(1H, dd, J=1.5, 7.5 Hz), 8.15-8.20(1H, m), 8.85(1H, d, J=5.1 Hz), 9.27(1H, s).	383
A0268	(CDCl ₃): 3.00(1H, dd, J=10.5, 12.6 Hz), 3.10-3.35(3H, m), 3.50-3.70(5H, m), 4.03(1H, dd, J=2.4, 10.5 Hz), 7.32(4H, m), 7.50(1H, s), 8.15(1H, dd, J=1.2, 5.1 Hz), 8.87(1H, d, J=5.1 Hz), 9.27(1H, d, J=1.5 Hz).	383
A0269	3.40-3.50(2H, m), 3.45(3H, s), 3.53-3.65(2H, m), 3.87-3.97(2H, m), 4.68(1H, t, J=10.2 Hz), 7.05(1H, s), 7.59(2H, d, J=11.1 Hz), 7.75(2H, d, J=11.1 Hz), 8.22(1H, dd, J=1.5, 5.4 Hz), 9.02(1H, d, J=5.1 Hz), 9.31(1H, s), 9.83(1H, d, J=9.6 Hz), 10.11-10.25(1H, m)(DMSO-d6)	383
A0274	(DMSO-d ₆): 3.45(3H, s), 3.40-3.70(4H, m), 3.92(2H, t, J=14.1 Hz), 4.67(1H, br s), 7.06(1H, s), 7.68(2H, d, J=10.0 Hz), 7.72(2H, d, J=10.0 Hz), 8.22(1H, d, J=4.8 Hz), 9.03(1H, d, J=4.8 Hz), 9.31(1H, s), 9.88(1H, br s), 10.22(1H, br s).	427
A0289	3.38-3.57(4H, m), 3.35(3H, s), 3.89(3H, s), 3.91-3.97(2H, m), 4.84-4.94(1H, m), 7.06(1H, s), 7.08-7.15(1H, m), 7.18(1H, d, J=8.4 Hz), 7.41-7.49(1H, m), 7.68(1H, d, J=7.6 Hz), 8.25(1H, d, J=4.9 Hz), 9.04(1H, d, J=5.1 Hz), 9.32(1H, s)(DMSO)	379
A0290	(DMSO-d ₆): 3.40-3.75(7H, m), 3.92(2H, t, J=13.2 Hz), 4.64(1H, t, J=9.1 Hz), 7.00-7.10(2H, m), 7.23(1H, d, J=7.6 Hz), 7.35(1H, s), 7.42(1H, t, J=7.8 Hz), 8.23(1H, d, J=5.6 Hz), 9.02(1H, d, J=5.2 Hz), 9.32(1H, s), 9.65-9.80(1H, brd), 9.90-10.15(1H, brd).	379
A0291	(DMSO-d ₆): 3.42(3H, s), 3.36-3.58(4H, m), 3.79(3H, s), 3.83-3.95(2H, m), 4.61(1H, m), 7.05(1H, s), 7.07(2H, d, J=8.1 Hz), 7.60(2H, d, J=8.7 Hz), 8.22(1H, dd, J=5.1, 1.2 Hz), 9.02(1H, d, J=5.4 Hz), 9.31(1H, s), 9.58-9.74(2H, m).	379
A0294	1.31(3H, t, J=6.8 Hz), 3.44-3.59(2H, m), 3.48(3H, s), 3.87-3.97(2H, m), 4.09-4.20(2H, m), 4.80-4.91(1H, m), 7.06(1H, s), 7.09-7.17(2H, m), 7.44(1H, t, J=7.4 Hz), 7.64(1H, d, J=7.5 Hz), 8.23(1H, d, J=5.3 Hz), 9.03(1H, d, J=5.2 Hz), 9.32(1H, s), 9.49-9.60(2H, m)(DMSO-d6)	393
A0304	(DMSO-d ₆): 3.45(3H, s), 3.64(3H, m), 3.93(3H, m), 4.78(1H, t, J=9.6 Hz), 7.13(1H, s), 7.97(2H, d, J=8.7 Hz), 8.01(2H, d, J=8.7 Hz), 8.43(2H, d, J=6.2 Hz), 8.93(2H, d, J=6.2 Hz), 10.12(1H, s), 10.70(1H, s).	374
A0331	(CDCl ₃): 2.00(4H, m), 3.05(1H, t, J=11.7 Hz), 3.18-3.30(3H, m), 3.29(4H, m), 3.56(3H, s), 3.62(2H, m), 3.91(1H, d, J=8.4 Hz), 6.57(2H, d, J=8.7 Hz), 7.31(3H, m), 8.17(1H, dd, J=1.2, 5.1 Hz), 8.85(1H, d, J=5.1 Hz), 9.27(1H, d, J=1.2 Hz).	418

A0337	(CDCl ₃):3.02(1H,dd,J=10.8,12.6Hz), 3.18(8H,m), 3.56(3H,s), 3.61(1H,t,J=9.0Hz), 3.87(4H,m), 3.95(1H,dd,J=2.7,10.8Hz), 6.93(2H,d,J=8.9Hz), 7.31(1H,s), 7.36(2H,d,J=8.9Hz), 8.16(1H,dd,J=1.5,5.4Hz), 8.85(1H,d,J=5.4Hz), 9.27(1H,d,J=1.5Hz).	434
A0340	(CDCl ₃):2.36(3H,s), 2.59(4H,m), 3.02(1H,t,J=11.4Hz), 3.16-3.29(7H,m), 3.26(3H,s), 3.61(2H,m), 3.94(1H,d,J=8.0Hz), 6.94(2H,d,J=8.7Hz), 7.31(1H,s), 7.34(2H,d,J=8.7Hz), 8.16(1H,d,J=5.1Hz), 8.85(1H,d,J=5.1Hz), 9.27(1H,s).	447
A0361	3.39-3.50(2H, m), 3.47(3H, s), 3.61-3.73(1H, m), 3.78(3H, s), 3.83(3H, s), 3.87-3.92(3H, m), 4.92(1H, t, J=10.5 Hz), 6.99-7.11(3H, m), 7.57(1H, d, J=2.7 Hz), 8.25(1H, dd, J=1.2, 5.1 Hz), 9.03(1H, d, J=4.8 Hz), 9.31(1H, d, J=0.9 Hz), 9.78(1H, d, J=9.0 Hz), 10.21-10.38(1H, m)(DMSO-d ₆)	409
A0362	(DMSO-d ₆): 3.47(3H, s), 3.37-4.04(6H, m), 3.94(6H, s), 5.09(1H, m), 6.82(2H, d, J=8.4Hz), 7.05(1H, s), 7.45(1H, t, J=8.4Hz), 8.22(1H, m), 8.24(1H, dd, J=5.4, 1.5Hz), 9.05(1H, d, J=5.1Hz), 9.32(1H, s), 10.06(1H, m).	409
A0366	3.38-3.60(4H, m), 3.47(3H, s), 3.88-3.95(2H, m), 3.90(3H, s), 4.86-4.92(1H, m), 6.96-7.01(1H, m), 7.06(1H, s), 7.12(1H, d, J=8.8 Hz), 7.71-7.79(1H, m), 8.23-8.24(1H, m), 9.03(1H, d, J=5.1 Hz), 9.32(1H, d, J=1.2 Hz), 9.55-9.72(2H, m)(DMSO)	397
A0367/ A0368	(DMSO-d ₆):3.30-3.75(7H,m), 3.80-4.00(5H,m), 4.80-5.00(1H,m), 6.93-7.00(1H,m), 7.05(1H,s), 7.11(1H,dd,J=2.4,11.4Hz), 7.84(1H,m), 8.23(1H,d,J=5.1Hz), 9.03(1H,d,J=5.1Hz), 9.31(1H,s), 9.60-9.80(1H,brd), 9.90-10.15(1H,brd).	397
A0370	3.31-3.56(3H, m), 3.45(3H, s), 3.69-3.78(1H, m), 3.90-3.99(2H, m), 3.94(3H, s), 4.95-5.03(1H, m), 6.96-7.02(1H, m), 7.03-7.09(2H, m), 7.49-7.56(1H, m), 8.24(1H, d, J=4.4 Hz), 8.51-8.69(1H, m), 9.03(1H, d, J=5.1 Hz), 9.32(1H, s), 10.55-10.67(1H, m) (DMSO)	397
A0378	2.77(1H, dd, J=10.5, 12.0 Hz), 3.18-3.30(3H, m), 3.61(3H, s), 3.64-3.71(2H, m), 3.86(3H, s), 4.37(1H, dd, J=2.1, 10.1 Hz), 6.89(1H, d, J=1.7 Hz), 6.99(1H, dd, J=1.6, 8.2 Hz), 7.32(1H, s), 7.50(1H, d, J=8.2 Hz), 8.19(1H, d, J=5.2 Hz), 8.86(1H, d, J=5.2 Hz), 9.27(1H, s)(CDCl ₃)	413
A0399	(CDCl ₃):2.76(1H,dd,J=10.2,12.3Hz), 3.10-3.40(3H,m), 3.55-3.80(5H,m), 3.85(3H,s), 4.39(1H,dd,J=2.4,10.2Hz), 6.78(1H,d,J=8.7Hz), 7.32(1H,s), 7.39(1H,dd,J=2.7,8.7Hz), 7.72(1H,d,J=2.4Hz), 8.20(1H,dd,J=1.2,5.1Hz), 8.87(1H,d,J=5.1Hz), 9.27(1H,d,J=1.2Hz).	457
A0408	(CDCl ₃): 1.98-2.03(4H, m), 2.84(1H, m), 3.17-3.32(7H, m), 3.60(3H, s), 3.59-3.71(2H, m), 3.85(3H, s), 4.28(1H, d, 8.4Hz), 6.10(1H, d, J=1.8Hz), 6.18(1H, d, J=8.3Hz), 7.29(1H, s), 7.33(1H, d, J=8.4Hz), 8.21(1H, d, J=5.2Hz), 8.85(1H, d, J=5.2Hz), 9.27(1H, s).	448

A0409	(CDCl ₃):1.95-2.10(4H,m), 2.95-3.10(1H,m), 3.19-3.45(7H,m), 3.59(3H,s), 3.50-3.80(2H,m), 3.80(3H,s), 4.48(1H,dd,J=2.2,10.2Hz), 6.49(1H,dd,J=3.0,8.9Hz), 6.63-6.87(2H,m), 7.32(1H,s), 8.20(1H,dd,J=1.4,5.2Hz), 8.86(2H,d,J=5.2Hz), 9.27(1H,d,J=1.1Hz).	448
A0414	(CDCl ₃):3.14(2H,m), 3.22(1H,t,J=11.6Hz), 3.41(1H,t,J=11.6Hz), 3.82(2H,m), 3.83(3H,s), 3.88(3H,s), 4.58(1H,dd,J=3.1,11.0Hz), 6.51(2H,m), 7.32(1H,s), 8.19(1H,dd,J=1.5,5.3Hz), 8.86(1H,d,J=5.3Hz), 9.27(1H,d,J=1.5Hz).	415
A0423	(DMSO-d ₆):3.35-3.70(4H,m), 3.48(3H,s), 3.78(3H,s), 3.97(2H,m), 4.70(1H,m), 7.06(1H,t,J=7.7Hz), 7.07(1H,s), 7.15(1H,d,J=7.7Hz), 7.31(1H,d,J=7.7Hz), 7.39(1H,t,J=7.7Hz), 7.61(2H,d,J=8.1Hz), 7.70(2H,d,J=8.1Hz), 8.25(1H,d,J=4.5Hz), 9.07(1H,d,J=4.5Hz), 9.33(1H,s), 9.66(1H,br s).	455
A0425	(DMSO-d ₆):3.61(3H,m), 3.76(3H,s), 3.81(3H,s), 4.01(3H,m), 4.69(1H,t,J=9.9Hz), 7.05(2H,d,J=9.0Hz), 7.07(1H,s), 7.67(2H,d,J=9.0Hz), 7.76(4H,s), 8.24(1H,dd,J=1.2,5.1Hz), 9.03(1H,d,J=5.1Hz), 9.32(1H,d,J=1.2Hz), 9.79(1H,d,J=10.2Hz), 10.07(1H,s).	455
A0434	(DMSO-d ₆):3.30-3.70(4H,m), 3.42(3H,s), 3.96(2H,d,J=13.8Hz), 4.71(1H,t,J=11.3Hz), 7.06(1H,s), 7.33(2H,t,J=8.0Hz), 7.77(6H,m), 8.24(1H,d,J=5.4Hz), 9.03(1H,d,J=5.4Hz), 9.32(1H,s), 9.80(1H,d,J=8.7Hz), 10.03(1H,s).	443
A0442	3.43-3.59(2H, m), 3.48(3H, s), 3.63-3.75(2H, m), 3.97-4.01(2H, m), 4.80-4.86(1H, m), 7.06(1H, s), 7.60-7.64(2H, m), 7.86-7.88(1H, m), 7.95-8.00(2H, m), 8.05-8.07(1H, m), 8.24-8.27(2H, m), 9.02(1H, d, J=5.4 Hz), 9.32(1H, s), 10.01(1H, d, J=10.2 Hz), 10.30-10.41(1H, m)(DMSO-d ₆)	399
A0517	(CDCl ₃): 2.97(1H, dd, J=12.3, 10.5Hz), 3.18-3.28(5H, m), 3.58(3H, s), 3.59(1H, m), 3.77(1H, m), 4.27(1H, dd, 10.2, 2.7Hz), 4.62(2H, m), 6.89(1H, t, J=7.5Hz), 7.16(1H, m), 7.27(1H, m), 7.28(1H, s), 8.26(1H, dd, J=5.4, 1.5Hz), 8.86(1H, d, J=5.4Hz), 9.26(1H, s).	391
A0864	(DMSO-d ₆):3.15-3.35(1H,m), 3.38-3.50(4H,m), 3.70-4.30(9H,m), 5.00-5.20(1H,m), 7.00-7.10(2H,m), 7.10-7.20(1H,m), 7.30-7.50(6H,m), 8.15-8.20(1H,m), 8.30-8.40(1H,brd), 9.05(1H,d,J=5.1Hz), 9.31(1H,d,J=0.9Hz).	487
A1074	(CDCl ₃):1.80-2.40(3H, m), 3.12-3.34(4H, m), 3.39-4.20(7.6H, m), 4.50-5.07(0.6H, m), 5.30-5.60(0.7H, m), 5.72-6.05(0.1H, m), 6.52-6.80(2H, m), 6.82-7.22(1H, m), 7.28(1H, s), 8.18(1H, d,J=4.8Hz), 8.89(1H, d,J=5.1Hz), 9.28(1H, d,J=1.2Hz)	439
A1339	(CDCl ₃):2.50-2.62(1H,m), 2.80-2.95(1H,m), 3.02-3.20(1H,m), 3.25-3.40(1H,m), 3.50-3.74(5H,m), 3.75-3.80(1H,m), 3.85(3H,s), 6.60-6.80(2H,m), 7.30(1H,s), 7.48(1H,t,J=8.4Hz), 8.19(1H,dd,J=1.2,5.1Hz), 8.86(1H,d,J=5.1Hz), 9.27(1H,d,J=1.5Hz).	411

A1340/ A1341	(DMSO-d6): 2.55(3H, d, J=3.9 Hz), 3.40-3.80(3H, m), 3.45(3H, s), 3.80-4.15(6H, m), 4.85-5.15(1H, m), 6.90-7.05(1H, m), 7.05(1H, s), 7.13(1H, dd, J=2.4, 11.4 Hz), 8.21(1H, dd, J=1.2, 5.1 Hz), 9.04(1H, d, J=5.1 Hz), 9.31(1H, d, J=1.2 Hz), 11.50-12.20(1H, brd).	411
B013	1.31-1.46(1H, m), 1.60-1.96(3H, m), 2.17-2.30(1H, m), 2.89-3.02(2H, m), 3.41(3H, s), 3.61(1H, d, J=12.4 Hz), 3.80(1H, d, J=13.5 Hz), 3.90-4.01(2H, m), 6.89-7.01(3H, m), 6.96(1H, s), 7.27-7.32(2H, m), 8.18(1H, d, J=4.4 Hz), 8.96(1H, d, J=5.0 Hz), 9.28(1H, s)(DMSO-d6)	378
B014	1.33-1.49(1H, m), 1.60-1.93(3H, m), 2.20-2.32(1H, m), 2.89-3.04(2H, m), 3.41(3H, s), 3.63(1H, d, J=13.3 Hz), 3.82(1H, d, J=11.1 Hz), 4.22-4.37(2H, m), 6.95(1H, s), 7.51-7.56(2H, m), 7.65-7.70(1H, m), 8.00-8.03(2H, m), 8.17(1H, dd, J=1.1, 5.1 Hz), 8.87(1H, d, J=5.1 Hz), 9.28(1H, d, J=1.0 Hz)(DMSO-d6)	406
B048	(CDCl3): 1.93-2.07(3H, m), 2.38(1H, m), 3.09(1H, m), 3.46(1H, m), 3.57(3H, s), 3.61-3.70(2H, m), 4.05(1H, m), 7.26-7.34(2H, m), 7.59-7.61(2H, m), 7.76(1H, m), 8.16(1H, m), 8.83(1H, m), 9.27(1H, s).	389
B049	(CDCl3): 1.92-2.08(3H, m), 2.36(1H, m), 3.11(1H, m), 3.44(1H, dd, J=12.9, 10.8 Hz), 3.58(3H, s), 3.61-3.70(2H, m), 4.06(1H, m), 7.11(1H, m), 7.28-7.33(2H, m), 7.70(1H, dd, J=8.7, 4.8 Hz), 8.15(1H, m), 8.86(1H, d, J=5.4 Hz), 9.28(1H, s).	407
B050	1.93-2.11(3H, m), 2.33-2.45(1H, m), 3.08-3.16(1H, m), 3.46(1H, dd, J=11.4, 12.9 Hz), 3.59(3H, s), 3.62-3.71(2H, m), 4.06(1H, d, J=12.6 Hz), 7.32-7.37(1H, m), 7.32(1H, s), 7.57-7.64(2H, m), 7.75(1H, d, J=8.1 Hz), 8.16(1H, dd, J=1.2, 5.4 Hz), 8.84(1H, d, J=4.8 Hz), 9.28(1H, d, J=0.9 Hz)(CDCl3)	389
B051	1.91-2.11(3H, m), 2.35-2.43(1H, m), 3.08-3.16(1H, m), 3.42-3.50(1H, m), 3.59(3H, s), 3.62-3.71(2H, m), 4.05(1H, d, J=11.1 Hz), 7.32(1H, s), 7.33-7.37(1H, m), 7.57-7.65(2H, m), 7.75(1H, d, J=7.8 Hz), 8.16(1H, d, J=5.7 Hz), 8.84(1H, d, J=5.4 Hz), 9.28(1H, d, J=1.2 Hz)(CDCl3)	389
B130	1.78-1.96(4H, m), 2.73-2.90(1H, m), 3.02-3.09(2H, m), 3.46(3H, s), 3.84(2H, d, J=12.6 Hz), 6.98(1H, s), 7.11-7.17(2H, m), 7.33-7.38(2H, m), 8.25(1H, d, J=5.1 Hz), 9.01(1H, d, J=4.8 Hz), 9.30(1H, s)(DMSO-d6)	366
B157	1.90-2.05(2H, m), 2.18-2.35(2H, m), 2.92-3.09(1H, m), 3.10-3.23(2H, m), 3.58(3H, s), 3.72-3.83(2H, m), 6.95-7.07(1H, m), 7.22(1H, dd, J=2.2, 9.0 Hz), 7.34(1H, s), 7.46(1H, s), 7.48-7.55(1H, m), 8.20(1H, d, J=5.3 Hz), 8.88(1H, d, J=5.2 Hz), 9.29(1H, s)(CDCl3)	406
B158	1.91-2.04(2H, m), 2.23(2H, d, J=8.9 Hz), 2.44(3H, s), 2.97-3.11(1H, m), 3.16(2H, dd, J=11.1, 12.4 Hz), 3.58(3H, s), 3.77(2H, d, J=13.0 Hz), 7.12(1H, d, J=8.5 Hz), 7.36-7.41(4H, m), 8.20(1H, d, J=5.3 Hz), 8.87(1H, d, J=4.8 Hz), 9.28(1H, s)(CDCl3)	402

B159	1.93-2.05(2H, m), 2.23(2H, d, J=12.6Hz), 3.19(3H, m), 3.58(3H, s), 3.81(2H, d, J=13.2Hz), 7.12-7.16(1H, m), 7.26(1H, s), 7.34(1H, s), 7.56(1H, dd, J=2.4, 8.7Hz), 7.77-7.76(1H, m), 8.20(1H, dd, J=1.2, 5.1Hz), 8.87(1H, d, J=5.1Hz), 9.29(1H, s) (CDCl ₃)	422
B160	2.01-2.22(5H, m), 3.20(2H, dd, J=1.4, 11.7Hz), 3.47(3H, s), 3.84(2H, d, J=13.2Hz), 6.99(1H, s), 7.32(1H, m), 7.72(1H, dd, J=2.1, 9.0Hz), 8.09(1H, dd, J=2.7, 9.1Hz), 8.27(1H, m), 9.01(1H, d, J=5.1Hz), 9.31(1H, d, J=1.5Hz) (DMSO-d ₆)	407
B162	2.13-2.43(4H, m), 3.10-3.38(3H, m), 3.57(3H, s), 3.65-3.83(2H, m), 7.30-7.40(3H, m), 7.45-7.59(1H, m), 7.62-7.80(1H, m), 8.10-8.22(1H, m), 8.88(1H, d, J=5.1Hz), 9.28(1H, s) (CDCl ₃)	389
B193	2.22-2.39(4H, m), 3.21-3.35(2H, m), 3.48(3H, s), 3.90(2H, d, J=13.5 Hz), 7.03(1H, s), 7.38-7.43(1H, m), 7.46-7.51(2H, m), 7.59-7.66(2H, m), 8.28(1H, d, J=5.0 Hz), 9.01(1H, d, J=5.0 Hz), 9.30(1H, s) (DMSO-d ₆)	373

【0058】

試験例：ウシ脳TPK1によるP-GS1リン酸化に対する本発明の医薬の阻害作用

反応系として、100mM MES-水酸化ナトリウム (pH 6.5)、1mM 酢酸マグネシウム、0.5mM EGTA、5mM β-メルカプトエタノール、0.02% ツイン20、10% グリセロール、12μg/ml P-GS1、41.7μM [γ-³²P] ATP (68kBq/ml)、ウシ脳TPK1、及び表に記載された化合物（被検化合物の溶液を10% DMSOの存在下で調製したことにより、最終の混合物は1.7% DMSOを含む）を含む混合物を用いた。ATP添加によりリン酸化反応を開始し、25℃で2時間反応させた後、氷上で21%過塩素酸を添加して反応を停止した。反応液を12,000rpmで5分間遠心し、P81ペーパー (Whatmann) に吸着させ、その後ペーパーを75mMリン酸で4回、水で3回、アセトンで1回洗浄した。ペーパーを乾燥して、残留した放射能を液体シンチレーションカウンターで測定した。結果を下記表に示す。被検化合物はTPK1によるP-GS1リン酸化を顕著に阻害した。この結果は、本発明の医薬がTPK1活性を阻害することによってAβの神経毒性及びPHFの形成を抑制すること、及び本発明の医薬がアルツハイマー病や上記疾患の予防及び／又は治療に有効であることを強く示唆している。

【0059】

【表4】

Table 4

Compound No.	IC ₅₀
A0262	8.2nM
A0263	12nM
A0264	8.6nM
A0264(HCl)	7.9nM
A0267	2.6 nM
A0268	1.1 nM
A0269	1.7nM
A0274	8.1nM
A0289	0.0018 μ M
A0290	6.7nM
A0291	3.5nM
A0294	20nM
A0304	7.4 nM
A0331	10 nM
A0337	7.4 nM
A0340	1.2 nM
A0361	0.82nM
A0362	1.5nM
A0366	0.00072 μ M
A0367	44nM
A0368	
A0367	0.25nM
A0368	
A0370	1.4nM
A0378	1.0 nM
A0399	0.71 nM
A0408	0.77nM
A0409	1.8 nM
A0414	1.7nM
A0423	15 nM
A0425	2.4 nM
A0434	3.4nM
A0442	2.5nM
A0517	1.5 nM

A0864	216 nM
A1074	1503 nM
A1339	26nM
A1340 A1341	374nM
A1340 A1341	34nM
B013	0.015 μ M
B014	0.0296 μ M
B048	0.00063 μ M
B049	0.0040 μ M
B050	0.00066 μ M
B051	0.0046 μ M
B130	0.036 μ M
B157	0.014 μ M
B162	0.0058 μ M
B193	0.14 μ M

【 0 0 6 0 】

製剤例

(1) 錠剤

下記の成分を常法に従って混合し、慣用の装置により打錠した。

実施例 1 の化合物	3 0 m g
結晶セルロース	6 0 m g
コーンスターチ	1 0 0 m g
乳 糖	2 0 0 m g
ステアリン酸マグネシウム	4 m g

【 0 0 6 1 】

(2) 軟カプセル剤

下記の成分を常法に従って混合し、軟カプセルに充填した。

実施例 1 の化合物	3 0 m g
オリーブ油	3 0 0 m g
レシチン	2 0 m g

【 0 0 6 2 】

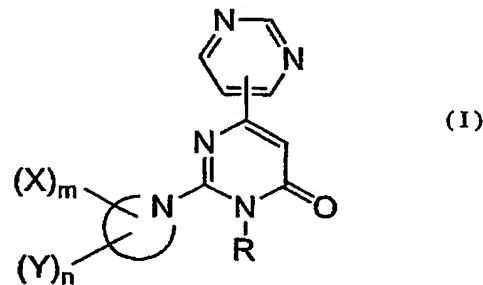
【発明の効果】

本発明の化合物は T P K 1 阻害活性を有しており、神経変性疾患（例えばアルツハイマー病）や上記他の疾患等の T P K 1 の異常昂進に起因する疾患の予防及び／又は治療のための医薬の有効成分として有用である。

【書類名】 要約書

【要約】 タウプロテインキナーゼ 1 の阻害活性を有する、下記式 (I) で表されるピリミドン誘導体若しくはその塩、又はそれらの溶媒和物若しくはそれらの水和物。

【化 1】



(式中、R は、置換されていてもよい $C_1 \sim C_{12}$ のアルキル基を示し；

【化 2】



はピペラジン環またはピペリジン環を示し；X はそれぞれ独立して、 $C_1 \sim C_8$ のアルキル基、一部が水素化されていてもよい $C_6 \sim C_{10}$ のアリール環、インダン環などを示し；m は 1 ないし 3 のいずれかの整数を示し；Y はそれぞれ独立して、ハロゲン原子、水酸基、シアノ基などを示し；X と Y、又は二つの Y 基が同じ炭素に結合している場合には、それらはそれぞれ結合して $C_2 \sim C_6$ のアルキレン基を形成してもよい。)

特願 2 0 0 3 - 1 2 6 0 2 2

出 願 人 履 歴 情 報

識別番号 [0 0 0 0 0 6 7 2 5]

1. 変更年月日 2 0 0 1 年 1 0 月 1 日

[変更理由] 住所変更

住 所 大阪府大阪市中央区平野町 2 丁目 6 番 9 号

氏 名 三菱ウェルファーマ株式会社

特願 2 0 0 3 - 1 2 6 0 2 2

出 願 人 履 歴 情 報

識別番号 [3 9 9 0 5 0 9 0 9]

1. 変更年月日 1 9 9 9 年 8 月 1 9 日

[変更理由] 新規登録

住 所 フランス 7 5 0 1 3 パリ、アヴェニュー・ドゥ・フランス 1 7 4
番

氏 名 サノフィー・サンテラボ